UNIVERSITY OF CALIFORNIA

Santa Barbara

Allenes, Alkenes & Alkynes: My Piece of the π

…in Water at Room Temperature…

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Daniel John Lippincott

Committee in charge:

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December 2018

The dissertation of Daniel J. Lippincott is approved.

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…the only things in Life we can know for certain,

are the things in which we do not know…

~ Plato and/or Socrates ~

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7) **Lippincott, D. J.**; Trejo-Soto, P. J.; Gallou, F.; Lipshutz, B. H. "Copper-Catalyzed Oxidative Cleavage of Electron-Rich Olefins in Water at Room Temperature" *Org. Lett.* **2018**, *20*, 5094.

6) **Lippincott, D. J.**; Linstadt, R. T. H.; Maser, M. R.; Gallou, F.; Lipshutz, B. H. "Synthesis of Functionalized 1,3-Butadienes *via* Pd-Catalyzed Cross-Couplings of Substituted Allenic Esters in Water at Room Temperature" *Org. Lett.* **2018**, *20*, 4719.

5) **Lippincott, D. J.**; Linstadt, R. T. H.; Maser, M. R.; Lipshutz, B. H. "Synthesis of Functionalized [3], [4], [5] and [6]Dendralenes through Palladium-Catalyzed Cross-Couplings of Substituted Allenoates" *Angew. Chem., Int. Ed.* **2017**, *56*, 847.

4) Handa, S.; **Lippincott, D. J.**; Aue, D. H.; Lipshutz, B. H. "Asymmetric Gold-Catalyzed Lactonizations in Water at Room Temperature" *Angew. Chem., Int. Ed.* **2014**, *53*, 10658.

3) Linstadt, R. T. H.; Peterson, C. A.; **Lippincott, D. J.**; Jette, C. I.; Lipshutz, B. H. "Stereoselective Silylcupration of Conjugated Alkynes in Water at Room Temperature" *Angew. Chem., Int. Ed.* **2014**, *53*, 4159.

2) Minkler, S. R. K.; Isley, N. A.; **Lippincott, D. J.**; Krause, N.; Lipshutz, B. H. "Leveraging the Micellar Effect: Gold-Catalyzed Dehydrative Cyclizations in Water at Room Temperature" *Org. Lett.* **2014**, *16*, 724.

Undergraduate

1) Lipski, R.; **Lippincott, D. J.**; Durden, B. C.; Kaplan, A. R.; Keiser, H. E.; Park, J.-H.; Levesque, A. A. "p53 Dimers Associate with a Head-to-Tail Response Element to Repress Cyclin B Transcription" *PLoS ONE* 7(*8*): e42615 (**2012**).

GRADUATE AWARDS

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- 1st prize poster award, at the *16th Annual French-American Chemical Society Conference*, **2016**

ABSTRACT

Allenes, Alkenes & Alkynes: My Piece of the π

…in Water at Room Temperature…

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Daniel John Lippincott

I. An environmentally responsible, mild method for the synthesis of functionalized 1,3-butadienes is presented. It utilizes allenic esters of varying substitution patterns, as well as a wide range of boron-based nucleophiles under palladium catalysis, generating $sp–sp^2$, $sp^2–sp^2$, and $sp^2–sp^3$ bonds. Functional group tolerance measured via robustness screening, along with room temperature and aqueous reaction conditions highlight the methodology's breadth and potential utility in synthesis.

II. A mild method for the synthesis of highly functionalized [3]–[6]dendralenes is reported, representing a general strategy to diversely substituted higher homologues of the dendralenes. The methodology utilizes allenoates bearing various substitution patterns, along with a wide range of boron and alkenyl nucleophiles that couple under palladium catalysis leading to sp-, sp^2-, and sp^3-substituted arrays. Regioselective transformations of the newly formed unsymmetrical dendralene derivatives are demonstrated. The use of micellar catalysis, where

water is the global reaction medium, and room temperature reaction conditions, highlights the green nature of this technology.

III. A copper-catalyzed oxidative cleavage of electron-rich olefins into their corresponding carbonyl derivatives is described as an alternative to ozonolysis. The scope includes various precursors to aryl ketone derivatives, as well as oxidations of enol ethers bearing atypical alkyl and dialkyl substitution, the first of their kind among such metal catalyzed alkene cleavage reactions. The use of an inexpensive copper salt, room temperature conditions, an aerobic atmosphere, and water as the global reaction medium highlight the green features of this new method. Associated mechanistic investigations are also presented.

TABLE OF CONTENTS

I. Synthesis of Functionalized 1,3-Butadienes *via* Pd-Catalyzed Cross-Couplings of Substituted Allenic Esters in Water at Room Temperature

"…all data, is good data…"

-yours truly

1.1 Introduction and Background

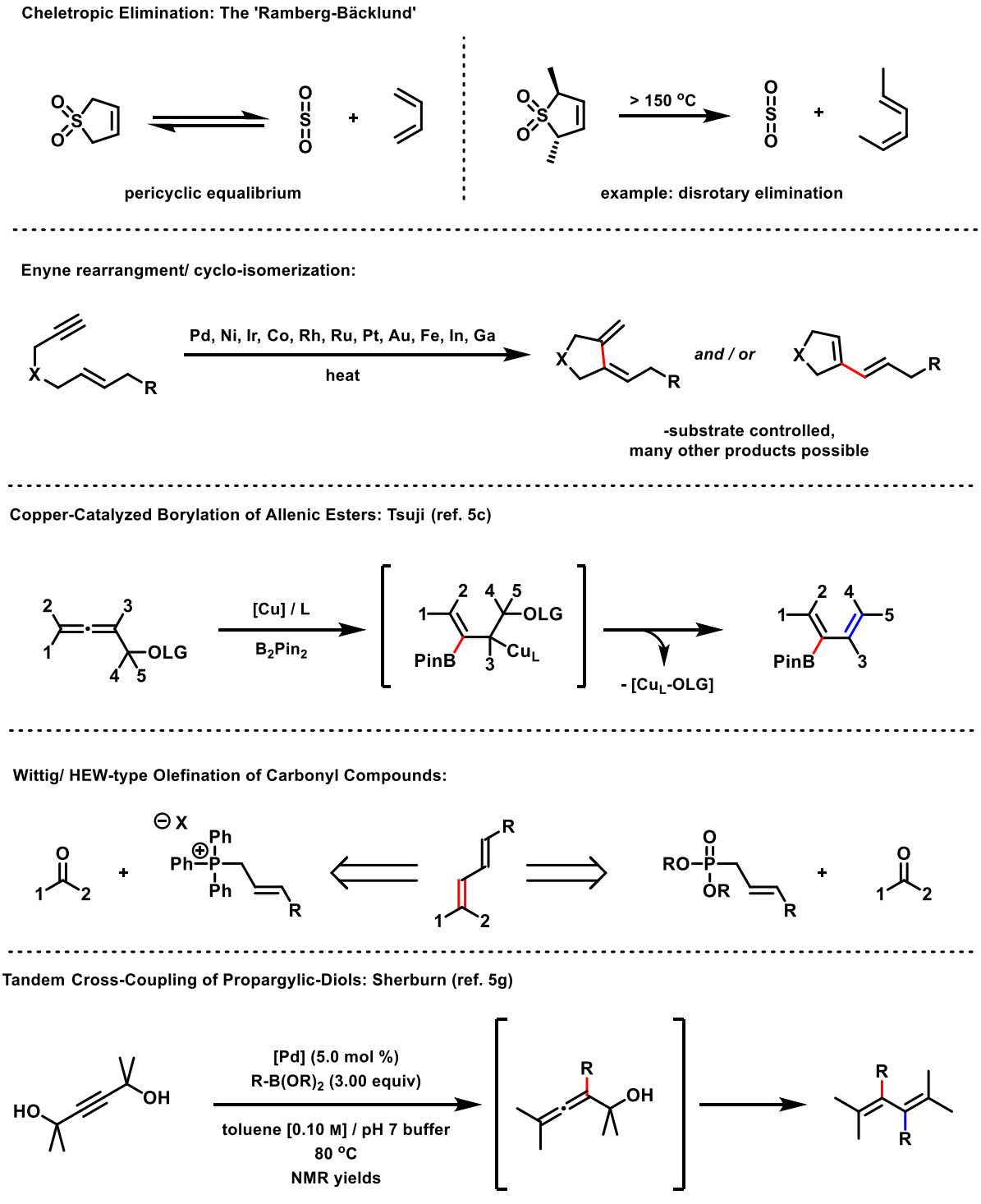
1,3-Butadienes have enjoyed a rich and thorough history throughout all disciplines of chemistry. Ranging from their use as polymerization monomers for the industrial production of synthetic materials for commerce,[1] to their use as electrophiles in various complexity building 1,2 and 1,4- addition reactions.[2] In their higher oligomeric forms (linear poly-butadienes) this motif has found unique utility by Nature acting as crucial components of dyes and pigments, a physical property which was adopted by industry in the direct application of electron transportation within conductive organo-photovoltaics and energy production/ shuttling.[3]

In organic synthesis, 1,3-butadienes have been un-waveringly relied upon in target-oriented syntheses as chemical pillars from which molecular complexity is generated. Selected examples of such utility include: epoxidations, regioselective conjugate additions, borylations, and in particular, [4 + 2] Diels-Alder reactions, with the latter being strong testimony, in and of itself, regarding their worth in synthesis.[2] Notwithstanding the exhaustive research devoted to understanding the reactivities of this functional group and the various disconnections

realized for their construction, there still remains room for improvement; specifically, their advancement into modern, and sustainable, organic chemistry.

Traditional inroads to 1,3-butadienes rely upon (1) elimination reactions; (2) reduction or isomerization of enynes; (3) enyne metathesis; (4) Wittig/HEW-type olefinations of conjugated carbonyl compounds; and (5) cross-coupling of alkenyl electrophiles and organometallics (Figure 1). However, while examples (1) – (4) are indeed time-honored reactions, these usually lead to varying levels of stereochemical control, as well as production of stoichiometric waste streams; both issues of which lead to tedious purification techniques often accompanied with diminished yields. While the latter example (5) is arguably the most modern among the examples illustrated, this route too has its own downside. Such issues that may arise include: use of 2-lithium or magnesium 1,3-butadienes, which are derived from the analogous, highly labile, 2-halo species;[4] the (assumed) necessity of organic solvents; alternative modes of catalysis leading to undesired side reactions/pathways; and the typical requirement of elevated temperatures and/or inert atmosphere conditions. Furthermore, high catalyst loadings are often accompanied within such methods that, generally, provide narrow or specific substrate scope. Thus, an advanced modernized approach, especially from an environmentally benign, green chemistry perspective, for accessing this prototypical functionality remains desirable.[5]

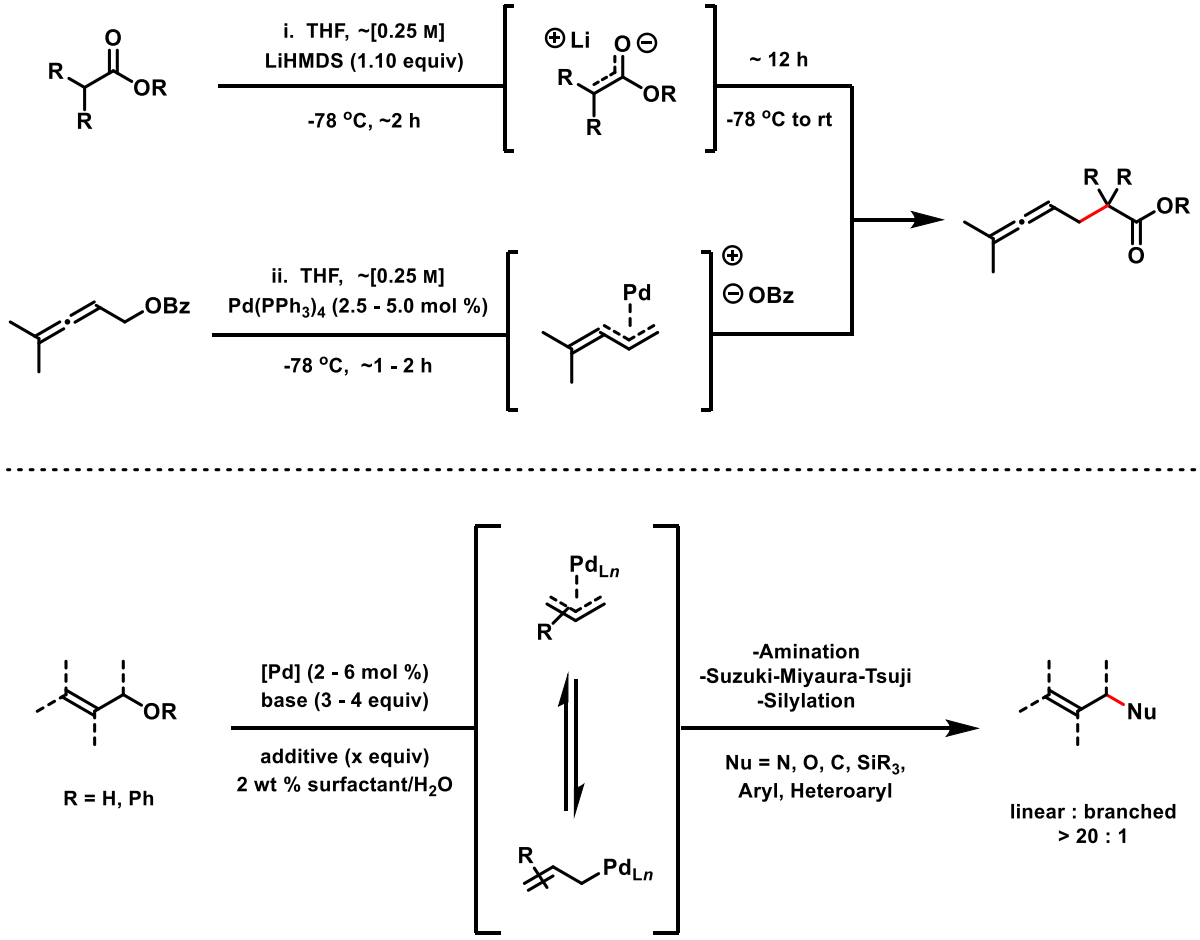
Figure 1. Selected Examples of Traditional 'in-roads' for Preparing 1,3-Butadienes



In nature their prevalence is demonstrated by the ever-increasing documentation of isolated natural products containing at least one butadiene group, thereby placing this class of moiety among the most commonly encountered, leading to sharp competition even with that of the annulenes (benzene in particular). Thus, if Nature has continually utilized this functionality, it would appear more than likely that synthetic chemists will also continue to do the same.

Inspired by the chemistry conducted during my work on asymmetric lactonizations,[6] from my first personal experience working with allenes I quickly became quite infatuated with their olefinic array. Thus, with some extra allenic benzoate in my possession, I engaged in a pursuit of further functionalizing these electrophilic synthons in an attempt to develop a methodology for allene derivatization. These early presumptions weren't without merit, as our group had previously demonstrated the various uses of allylic ethers as competent reaction partners in cross-coupling reactions under our, modernized, micellar catalysis conditions (Scheme 1).[7] Applications of this approach were proven to be versatile, and readily applicable to a range of substitution adducts derived from boron, amine, silyl or carbon nucleophiles.

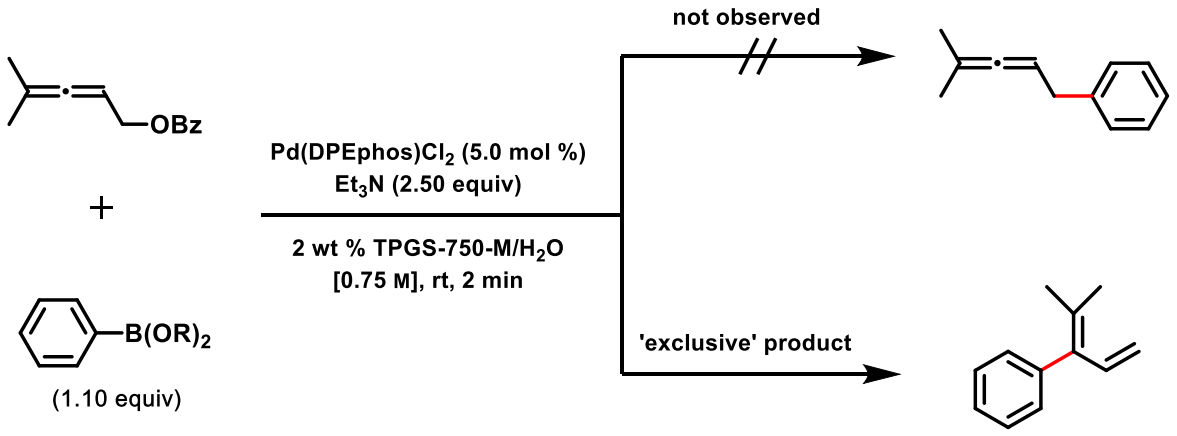
Scheme 1. General Route to Allenoates (top) & Prior Tsuji-Trost Art in Aqueous Media (bottom)



1.2. Results and Discussion

Given the above-mentioned successes, the use of an analogous allenic derivative was considered as an alternative electrophilic coupling partner for these Tsuji-Trost-like allylic displacements. Indeed, when tested in the presence of a boron nucleophile under related reaction conditions, a near instant, exothermic reaction resulted. However, upon product isolation it was revealed that with allenyl systems, coupling occurs exclusively at the central allenic carbon, resulting in formation of 2-substituted 1,3-butadienes as the exclusive product (Scheme 2, and Scheme 3, red).[8]

Scheme 2. Initial 'Serendipitous' Result

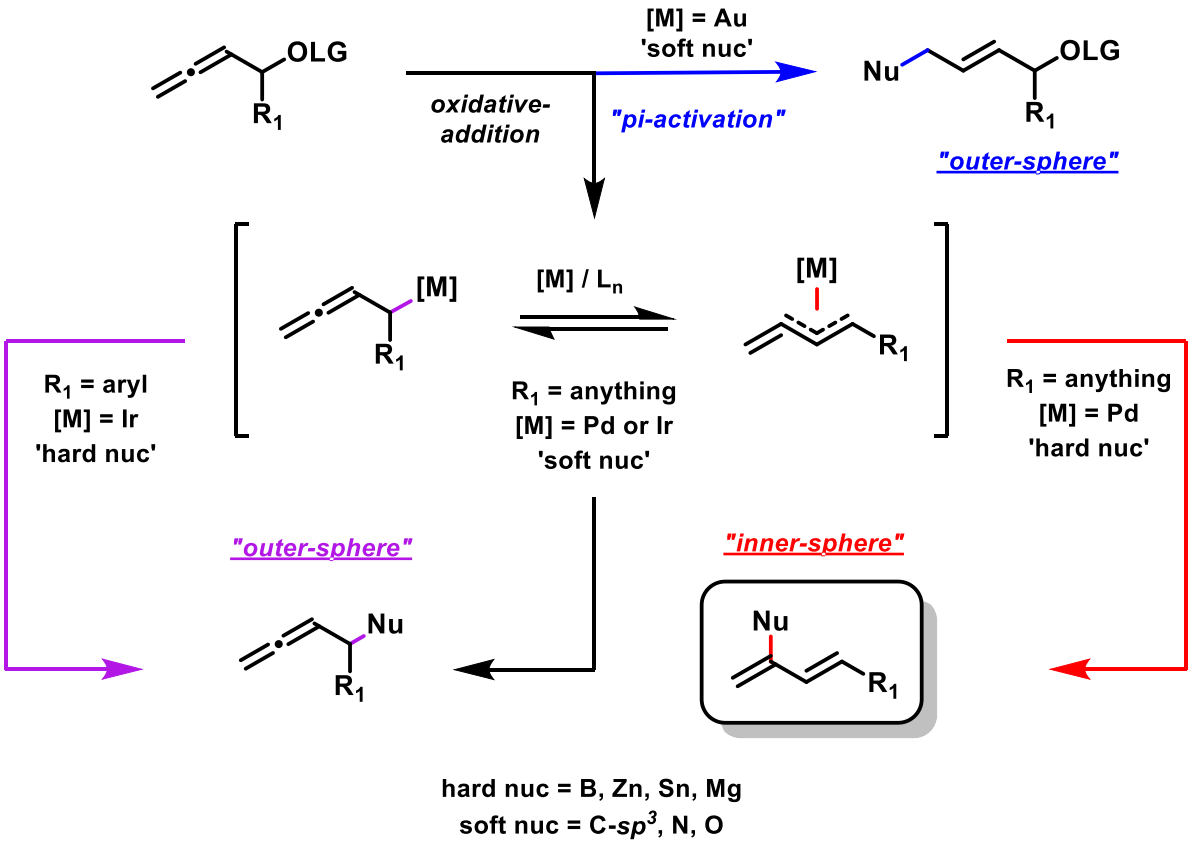


Conversely, use of iridium (in place of palladium) as catalyst and alkyl zincates (in place of boronates) as 'hard' nucleophiles, in closely related displacements of α-aryl substituted allenic esters, leads exclusively to allenic products of 'outer-sphere'-type retentive-substitution; as demonstrated recently by Carreira and co-workers (Scheme 3, purple).[9] While a strong improvement in asymmetric allene synthesis, the method was not without limitations: (1) the allene could only be mono-substituted specifically at the α-position; (2) this substituent must be an aryl group (and usually naphthyl); (3) yields were consistently in the modest-to-good

range; (4) heteroaromatics and nitrogen nuclei appear to not be tolerable to the reaction conditions.

Likewise, use of gold catalysis also gives rise to yet another distinctive course of reactivity.[10] Here, gold-mediated Lewis acidic π-activation of allenes affords alkyl allylic ethers through an intermolecular hydroalkoxylation mechanism with various alcohols (Scheme 3, blue). This is of note because even in the presence of an allenic benzoate leaving group, the regioselective nature of the reaction system retains this moiety; leading to linearly substituted allylic benzoates.

Scheme 3. Orthogonal Metal-Activation and Substitution of Allenyl Electrophiles



As demonstrated in Scheme 3, these differing reactivity patterns are thus a function of the nucleophile employed, proper choice of transition metal catalyst, the ligand chelating said metal, and to some extent the substitution pattern on the allenic ester; collectively the control of these distinguishing variables results in distinct and unique transition states, and therefore resulting products.

While Akira Suzuki himself had disclosed this particular Pd-catalyzed Suzuki-Miyaura transformation in 1994 leading to 1,3-butadienes, a narrow substrate scope of eight molecules was reported. Thus, within these few examples the extent of this reactions potential was left in an under-evaluated position; where the potential to incorporate hetero-atoms, useful functionality, and varying substitution patterns were all un-addressed. Taken wholly, it was therefore envisioned that a more in-depth study of this valuable transformation could help to: (1) further broaden the scope of this route to important conjugated dienes; (2) assess the ability to create C-C bonds of different hybridization beyond C-sp^2 nucleophiles; while at the same time (3) further document its utility under our *'modernized'* environmentally responsible aqueous reaction conditions.[11]

In fact, under our aqueous reaction conditions, the palladium catalyzed formation of functionalized 1,3-butadienes *via* cross-couplings of substituted allenic esters worked quite well from the start. Nearly every combination of substrate and palladium salt quickly and efficiently furnished the desired 1,3-butadienes in high yield; and minimal further work was needed to arrive at a set of optimized conditions.

Further screening of catalysts revealed that surprisingly, any palladium salt employed as catalyst cleanly promoted the desired transformation (optimization was conducted utilizing terminal-dimethyl substituted allenic benzoate and phenyl boronic acid). The only

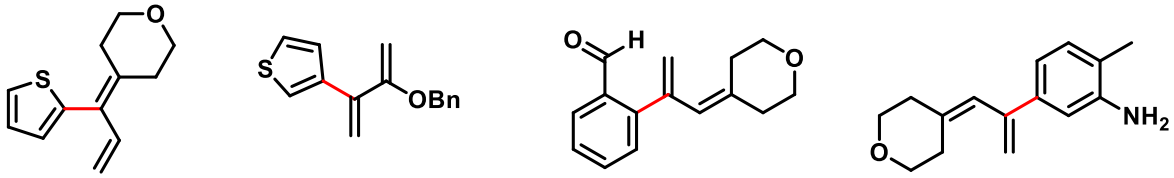
discrepancies between the palladium-salts screened were the amount of time required for full conversion of starting material. Time differences ranged from two minutes using ~ 1.0 mol % $Pd(DPEphos)Cl_2$, up to four hours using 5.0 mol % of 10 wt % Pd-on-charcoal; again for the model system. Conversely, catalysis did not occur in the presence of other transition metal salts such as Ni(II), Rh(I) or Rh(III); all of which resulted in no consumption of the starting allenic ester. It was found that a range of bases could be used successfully, such as KOH, K_3PO_4 or Et_3N; with triethylamine (Et_3N) being identified as the more superior. Although less than an equivalent of base could often be employed, when engaging particularly highly crystalline boron derivatives, the use of 2.50 equivalents was found to be generally sufficient across a wide range of coupling partners. Being organic in nature it is likely that Et_3N helps aid in the homogeneity of the reaction mixture not merely as a base but also acting, in some regard, as a co-solvent. Likewise, the nature of the leaving group was of little consequence. While acetate, methyl carbonate and benzoate where all found to engage equally efficient in the cross-coupling of the model system, the decision to employ the larger benzoate group, chosen as the ideal leaving group, provided substantial substrate stability; allowing for prolonged storage without observable decomposition over months-to-years. Whereas, the other derivatives (*e.g.* formates and acetates) were observed to slowly decompose over-time; even when stored under an inert atmosphere in the refrigerator. Furthermore; for relatively light, low molecular weight, hydrocarbon allenic esters (*e.g.* the parent, unsubstituted allenic ester) protection as the allenic benzoate aided in product monitoring (*i.e.* thin-layer-chromatography, or TLC analysis), as well as product isolation in the neat form without loss of material under high-vacuum.

As many of the initial products prepared were of low polarity, and of minimal incorporation of heteroatoms, separation from protodeborylated materials arising from an excess of boron coupling partner employed at the beginning of this work, was occasionally problematic due to over-lapping TLC spots and column chromatography fractions. Gratifyingly, by simply running the reactions with 1.00 – 1.05 equivalents of boron reagent resolved these potential issues, leading to an improved reaction impurity profile, yet, without adversely affecting isolated yields.

With optimized conditions in hand, the breadth of the arrived at methodology was assessed with regard to: (1) substitution patterns and functionality appended to the allenic ester educts (compared to the seminal report from Suzuki);[11a] (2) the various types of boron species utilizable; (3) the extent of functionality and substitution contained within the boron-based coupling partner (Scheme 4).

Scheme 4. Representative Scope of sp^2-sp^2 Bond Formations

sp^2-sp^2 connections

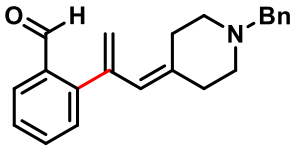


1 $B(OH)_2$, 81%

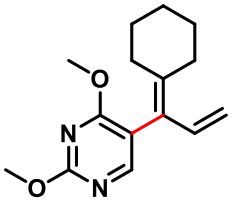
2 $B(OH)_2$, 89%

3 $B(OH)_2$, 88%

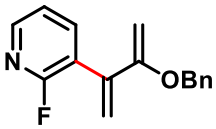
4 $B(OH)_2$, 84%



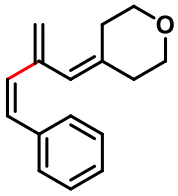
5 $B(OH)_2$, 72%



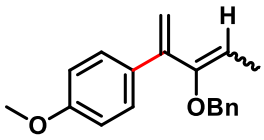
6 B(MIDA) , 77%



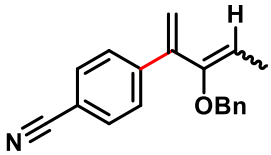
7 $B(OH)_2$, 84%



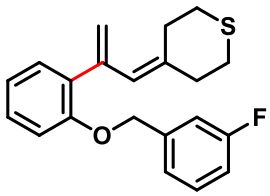
8 *(Z)*-BPin , 71%



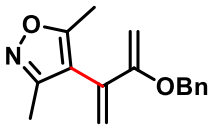
9 $B(OH)_2$, 81%
(E:Z) ~1:9



10 $B(OH)_2$, 79%
(E:Z) ~1:9

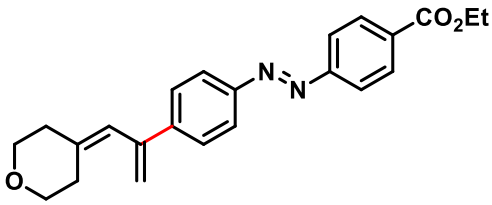


11 $B(OH)_2$, 90%

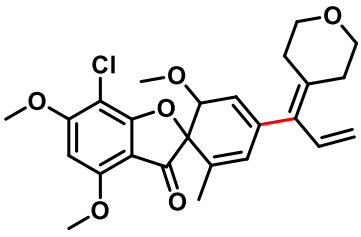


12 $B(OH)_2$, 97%

13 $PhMe_2Si$-BPin, 75%



14 BPin , 94%



15 BPin , 74%

As shown in Scheme 4, boronic acid, *N*-methyliminodiacetic acid (B(MIDA)), and pinacol esters (BPin) were all viable boron-containing partners; as well, substitution at *any* of the allenic carbons was also equally tolerated. Whereas these tolerations and generalities were not documented in Suzuki's report,[11a] and shown not to be amenable to Carreira's method,[9a] resulting in unfortunately low substitution in their resulting substrate scopes. Within the array of boron educts analyzed both steric and electronic demands were assessed. Thus, aryl rings containing *ortho-, meta-*, and *para*-substituents were all equally suitable, their success being independent of their either electron-donating or electron-withdrawing nature.

Gratifyingly, these cross-couplings were not limited to simple aryl boron derivatives, where it was quickly found that heteroaromatics also proceeded smoothly with hetero-residues such as thiophenes (at either their 2 or 3 position), pyrimidines, pyridines and even isoxazoles, leading to products **1**, **2**, **6**, **7**, and **12**; respectively. The use of an unsymmetrical allenic ester as educt raised the question of resulting *E-Z* stereo-chemistry in resulting 1,3-butadiene adducts **9** and **10**. Here, although selectivity was not perfect the couplings proceeded in high conversion to afford roughly ~1:9 (*E:Z*) ratios, irrespective of electronic effects (donating *vs*. withdrawing substituents). Although a large set of palladium salts and ligands were assessed in an attempt to further control the stereochemical outcome of these 'unsymmetrical' cross-couplings, unfortunately an exclusive system remained elusive; a problem that is still, as of yet, unsolved.

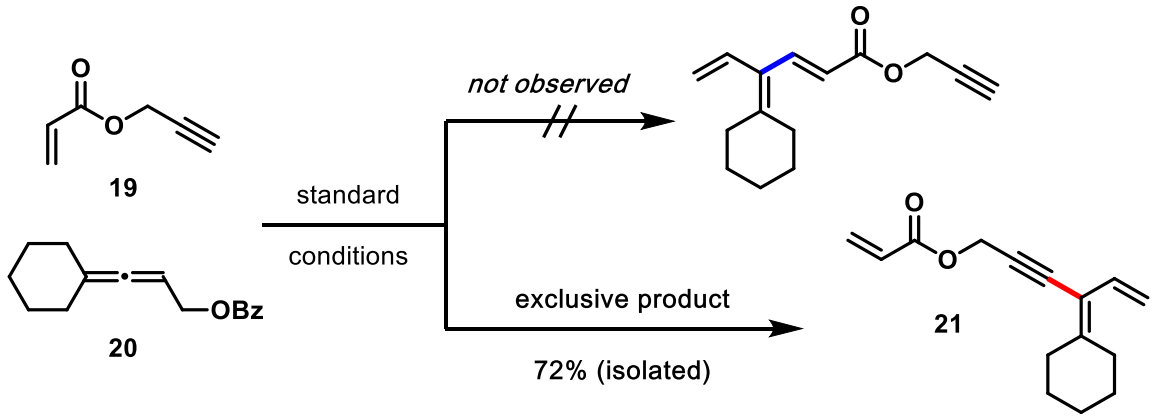
Having exhausted nearly all the commercially available boron species the group had to offer at that time (which were scarce to say the least) it seemed time to start making others, not only to enhance the 'attractiveness' of the current substrate scope, but also in an attempt to showcase the utility of the method in real-world contexts; while having a little fun on the side (of course).

Although, moderate stereo-selectivity was observed with racemic allenic ester educts (*i.e.* leading to products **9** and **10**), the question of stereo-retention of pre-defined reagents, engaging in C-C bond formation, was confirmed to be high as demonstrated with the success of substrate **8**. This example is two-fold noteworthy because of the ability to: (1) couple a stereo-defined *(Z)*-vinylboronate with complete retention of the initially set olefin-geometry, as well as, (2) an unprecedented, selective, synthesis of a stereo-defined-(*Z*)-[3]dendralene (see Chapter II for a thorough discussion on [*n*]dendralenes). Due to Suginome's reagent's rapid and ready participation in our group's prior silylcupration studies,[12] along with the ease of activating the silicon-boron (Si-B) bond allowing for facile transmetallation, it was envisioned that its employment may also be amendable to the currently developed reaction conditions. Indeed, use of Suginome's ($PhMe_2Si$-BPin) reagent quickly and smoothly led to butadienyl-silane **13** in good yield. The yield can, and should, most likely be close to quantitative; however, at the time our house-made reserves had ran out. Silylated C-sp^2 compounds are of synthetic utility due to their ability to engage in Hiyama-Denmark cross-couplings[13] as well as their ability to serve as 'masked' halide-equivalents.[14] An azobenzene, derived from benzocaine, also participated exceptionally well readily providing adduct **14** in high isolated yield. This example is of particular note due to the controllable photo-isomerization capacity of azobenzenes, leading to an operationally simple procedure for derivatizing bathochromic shifted photoactive materials which are recently 'hot' targets for their multitude of utilities. Specific examples of their more recent applications include their employment as small molecule photo-switches for use in materials chemistry, organo-photovoltaics, and in particular the new and quickly growing field of photopharmacology.[15] Moreover, use of the 'thermodynamic' antifungal derivative of griseofulvin (W.H.O. list of essential medicines)[16]

led to the rapid construction of a potentially biologically active [4]dendralenic derivative **15**, containing multiple appended functional handles, readily available to provide further construction of molecular complexity.

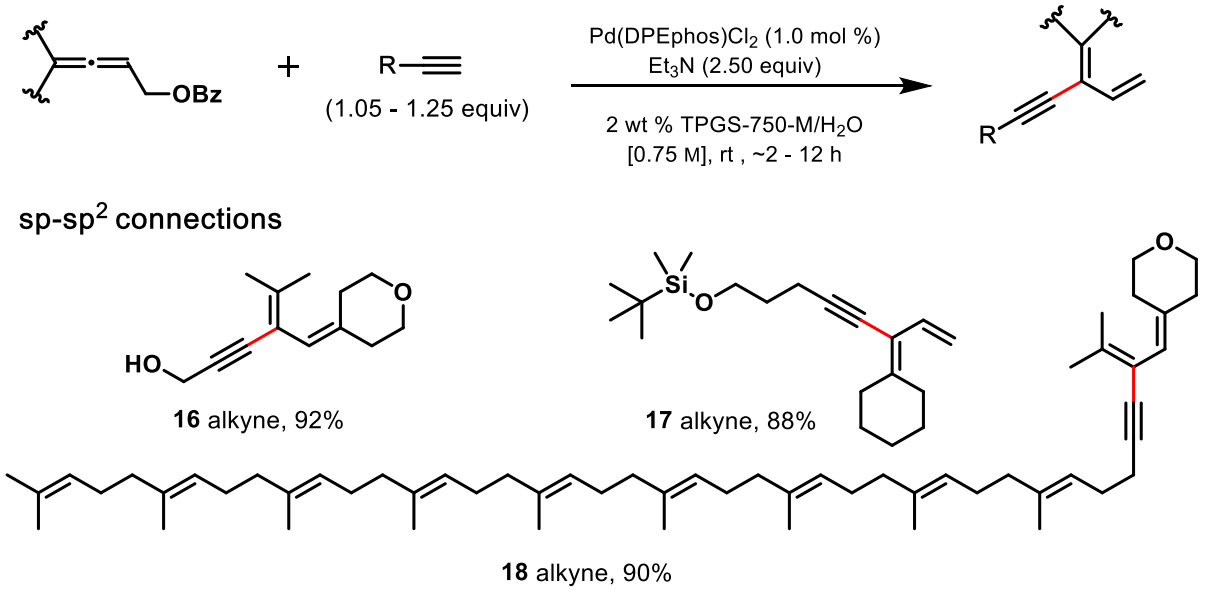
With a range of successful sp^2 bond formations achieved, attention next turned to the construction of bonds of different hybridization. Our research group has documented the ability to effect Sonogashira-type cross-couplings under micellar catalysis conditions, either utilizing the ligand cBRIDP[17a] or more recently at the ppm (parts-per-million) level of palladium when ligated to the 'super-ligand' HandaPhos.[17b] Although, the initial use of C_{sp}–BF_3K salts, prepared according to Molander's protocol,[18] under the 'standard-conditions' smoothly furnished the desired 2-alkynyl-1,3-butadienes in good yield the necessity to pre-functionalize the nucleophilic coupling partners, in this case, was a less than ideal situation. And in this vein, sometimes it's best to be lucky. Fore, in an effort to generate a [3]dendralene, *via* a Heck-type cross-coupling in the presence of a propargylic residue, a smooth reaction resulted and in high yield.

Scheme 5. Observation of Preferential Sonogashira *vs.* Heck Coupling



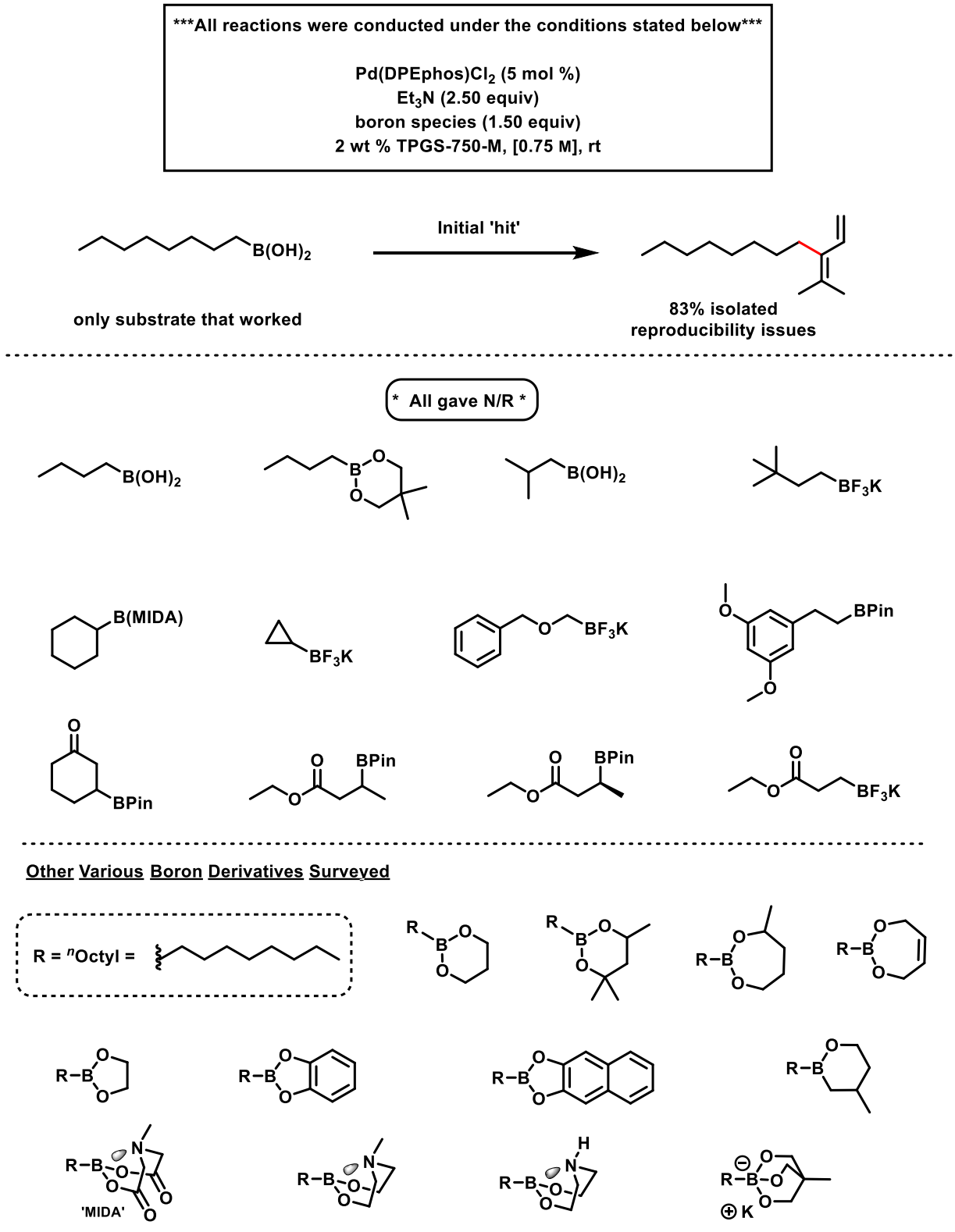
Thus, it became apparent upon exploring the reactivity of acrylate **19** toward allenic ester **20** that not only was the preparation and use of an acetylenic boron precursor not required to effect a Sonogashira-type cross-coupling, but also that the nucleophilicity of terminal alkynes, relative to a competitive Heck-type pathway, was significantly higher under micellar catalysis conditions (Scheme 5, and Scheme 6). As model examples of this sp-sp^2 bond forming pathway silyl-protected and free, unprotected, acetylenic alcohols leading to products **17** and **16** were easily formed. Furthermore, solanesol alkyne, derived from solanesol (the most abundant polyprenoidal compound found in the stalks of tobacco plants),[19] also proceeded well to provide adduct **18**. This is of interest as the lipophilic moiety in the nonameric isoprenyl unit appears to not, itself, integrate into the synthetic micellar membrane; which would likely interfere with amphiphile aggregation, particle composition, and therefore reaction efficacy. Compared to the known catalysts/ligands employed in earlier Sonogashira work (*vide supra*), the ability to use a more common catalyst (Pd(DPEPhos)Cl_2 vs. Pd$(OAc)_2$/HandaPhos), in relatively low loadings, is suggestive of an increased electrophilic nature of *in situ* generated π-allenyl intermediates (*vide infra*).

Scheme 6. Representative Scope of sp-sp^2 Bond Formations



While establishing substrate scope, having demonstrated access to the relatively easier sp and sp^2 bond constructions, attempts employing alkyl (sp^3) boron nucleophiles led to mixed results. Initially, the use of *n*-octylboronic acid was successful, providing the desired butadiene in 83% isolated yield; however, this result was not always reproduceable. After this initial 'hit' the preparation and subsequent use of various boron species such as acids, pinacol esters, MIDA boronates, and BF_3K salts, of varying functionality, all failed to generate the desired results (Figure 2).

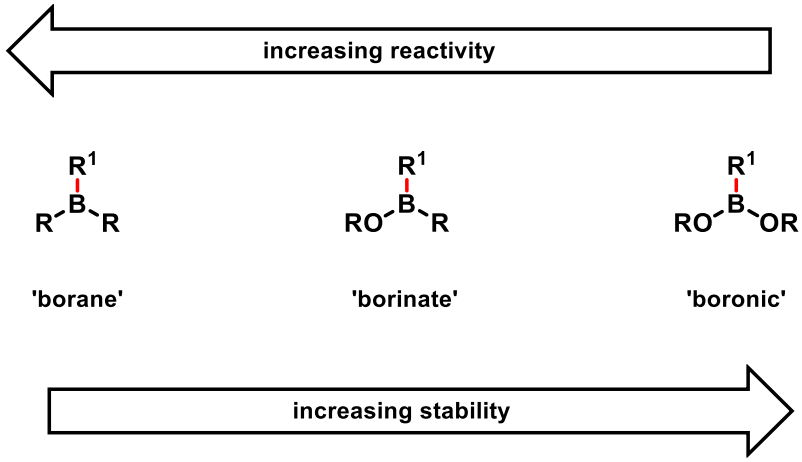
Figure 2. Various sp^3 Boron Species Prepared & Surveyed



Traditionally, the construction of sp^3 bonds in related cross-couplings (*via* Suzuki-Miyaura, Kumada, Negishi, *etc.*) rely upon strong organometallic reagents derived from either alkyl-boranes, lithiums, zincates, or Grignard (magnesium) reagents (usually formed *in situ*). However; the use of these significantly oxygen and/or moisture-intolerant species precluded even their attempt in our modernized aqueous platform. However, in these traditional examples, once the alkyl group had successfully been transferred to the metal center (transmetallation), the metal faithfully delivers the sp^3 group as desired. Thus, a new, or amended, equivalent was to be desired; with an aim at enhancing this transmetallation step, in particular.

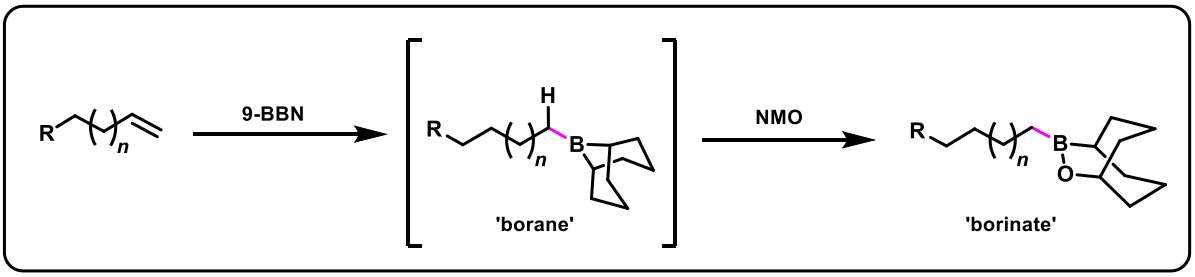
Fortunately, it was around the same time that my lab mate Roscoe 'T. Hadley' Linstadt became interested in the, yet un-solved, problem of alkyl delivery, in any regard, within the context of our groups aqueous reaction system.[20] While he initially was looking to controllably direct transmetallation of an appropriate boron-species onto copper, to ultimately provide access to alkyl-conjugate addition reactions, I on the other hand was becoming increasingly frustrated at the inability to simply cross-couple alkyl units. Thus, from two independent lines of inquisitive research (exhaustive exploration/ exploitation of allenes to dienes and investigating the preparation of exotic boron species) a common set of alkyl-issues resulted in an allegiance of sp^3 hybridized nature.

Figure 3. Structural Differences Between Boron Reagent Oxidation Levels



While Suzuki had demonstrated the use of 9-BBN derivatives (boranes) as viable reagents in his diene protocol,[11a] and although these species are tolerant to water, their inherent pyrophoric nature, low stability to oxidation (even upon brief exposure to air) and limited shelf-life made them unattractive reagents for our methodology. We, therefore, reasoned that the use of *borinate* derivatives as an intermediary between boronic acids and boranes might provide sufficient reagent stability and safety relative to boranes, while still retaining adequate electrophilicity, relative to boronic acids, to eventually lead to a two electron transmetallation.[21a] Soderquist and co-workers have previously shown that selective mono-oxidation of 9-BBN derivatives with TMANO (trimethylamine *N*-oxide) or NMO (4-methylmopholine *N*-oxide) leads to more robust boron species, *B*-alkyl-9-oxa-10-borabicyclo[3.3.2]-decane (R-OBBD), with improved air stability (see Figure 3, and 4).[21b]

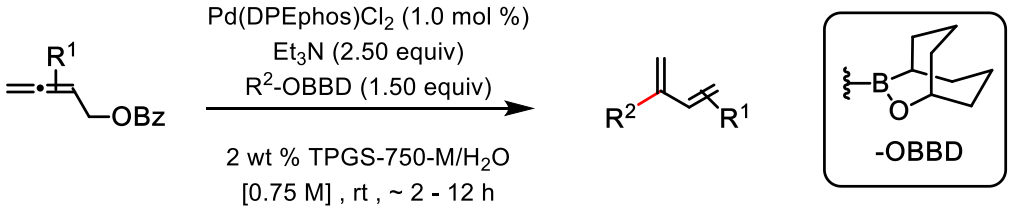
Figure 4. Mono-Oxidation of –9BBN Derivatives to Afford -OBBD Derivatives

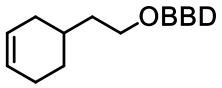
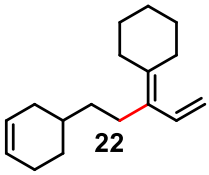
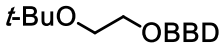
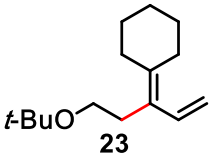
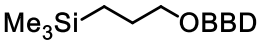
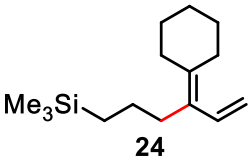
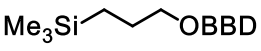
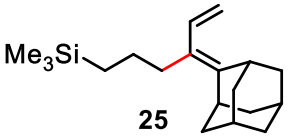
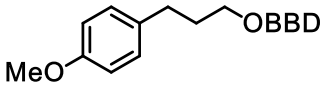
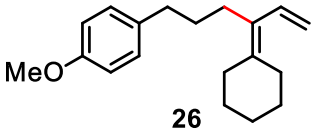
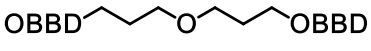
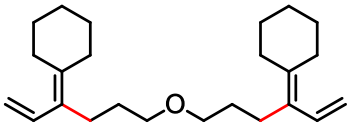
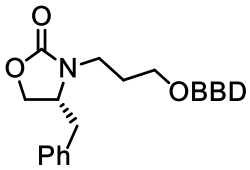
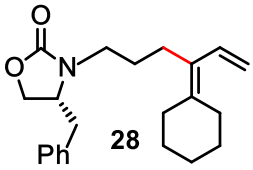
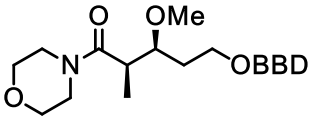
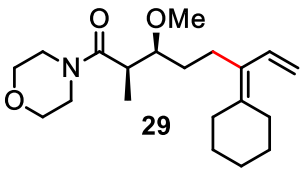


Gratifyingly, initial experiments with these newly prepared -OBBD reagents, using standard/ simple phenyl iodides as coupling partners, under aqueous micellar reaction conditions, led to smooth formation of the long sought-after sp^2-sp^3 carbon-carbon bonds. Now the only question remaining was: can they be utilized to prepare dienes? The answer is…. Yes !

Indeed, these -OBBD reagents promoted the construction of this difficult C-C bond (Table 1), due to their higher reactivity compared to boronic acids, as well as their increased stability relative to their corresponding 9-BBN derivatives, in our aqueous, open-to-air, system. Moreover; since our initial work performed on allenic ester systems[22] these reagents have, in their own regard, been fully optimized for our micellar catalysis platform by our youngest of naturally inquisitive chemists, Nicholas R. Lee.[21c]

Table 1. Representative Examples of sp^2-sp^3 Bond Formations *via* –OBBD Derivatives



entry	educt	1,3-diene product	isolated yield (%)
1		 **22**	54
2		 **23**	64 (48 h)
3		 **24**	65
4		 **25**	87
5		 **26**	94
6		 **27**	43
7	*(R) - (+)* 	 **28**	93
8		 **29**	77

As shown in Table 1, a broad range of sp^3 groups bearing useful synthetic functionalities all provided the corresponding dienes in modest to excellent yields, with minimal side product formation. The yields of entries 1-3 are diminished presumably due to high product volatility of the nearly pure-hydrocarbon adducts. To confirm this a direct comparison experiment was undertaken with use of a heavier allenic ester. Thus, entry 3 was evaluated against its analogous adamantyl derivative, which displayed no such problems in this regard (compare entries 3 and 4), confirming our hypothesis on volatility. Even the more exotic *bis*-nucleophile (entry 6) could be used, ultimately promoting a double sp^2-sp^3 cross-coupling sequence, to produce the bis-diene adduct **27** in a single operation. While convincing, and demonstrative of the quality of the bond being formed, the lack of 'obvious' utility of these alkyl-bond formations to 'real-life' synthetic scaffolds was still lacking. To this end, nucleophiles possessing carbonyl functionality, versatile synthetic handles (*e.g.* morpholino-Weinreb-amide), and chirality such as oxazolidinone (entry 7) and aldol adduct (entry 8) were synthesized and subjected to our standard reaction conditions. Pleasingly, both of these OBBD derivatives, also, cleanly coupled under the standard conditions, with no observable erosion in dr.[23] Showcasing our methods direct potential utility, in the context of complex molecule synthesis, and natural products synthesis, in particular.

Having demonstrated the ability to construct C-C bonds of any hybridization and with complete regio-control; we were still unsatisfied in regard to the over-all usefulness/attractiveness of the method. Therefore, an investigation was made so as to efficiently examine functional group compatibility. To this end, we became attracted to Glorious' recent contribution presenting his additive effect analysis; (*i.e.* a 'robustness screen') which is a method for establishing functional group tolerance. This simple technique has

emerged as a powerful tool to quickly and accurately predict the compatibility of larger and structurally more diverse coupling partners (*e.g.*, natural products) without having to engage precious and/or multi-step processes to prepare substrates for initial screenings.[24]

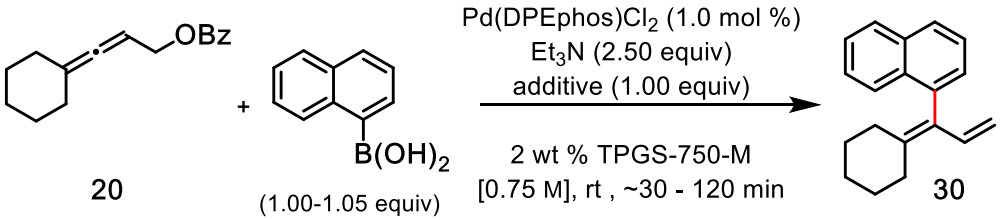
Traditionally these screenings are performed by running a positive control reaction, in the absence of any additive (standard reaction conditions). This same reaction is then repeated, as many times as desired, in the presence of various additive molecules, selected for various reasons, to ascertain whether a particular functionality (present in the additive molecule) affects the transformation under question in a positive, negative or neutral regard (enhancing, inhibitory or benign; respectively). Upon completion of the reaction, or as time points, these designations are ascribed after gas chromatography (GC) analysis, relative to an internal standard molecule. During such processes the need to set calibration curves for each additive tested, at specific concentrations, with the chosen internal standard, evidently results in only extrapolated data sets; and no *hard* data (ignoring real-life situations and effects of product separation, isolation and stability). However, after a given 'additive-reaction' is complete, if instead one was to simply run a column isolating *both* the desired compound along with the corresponding additive molecule, then the true breadth and 'hardiness' of the methodology and screening-set become truly representative.

Accordingly, un-biased allenic ester (**20**) was chosen and initially used in the absence of an additive to establish a base-line measure of reaction efficiency, with 1-naphthylboronic acid, leading to diene **30** (Table 2, entry 1). The same reaction was then repeated in the presence of one equivalent of an additive molecule bearing a functional moiety that either (a) required a lengthy synthesis to append onto the starting allenic ester, (b) is known to bind to and deactivate

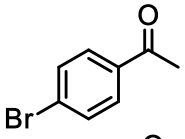
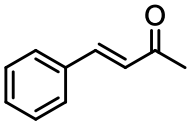
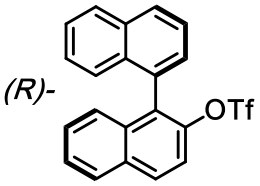
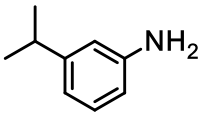
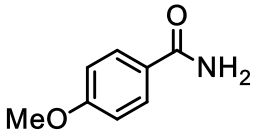
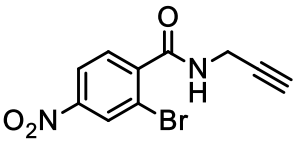
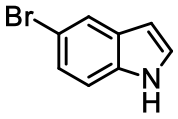
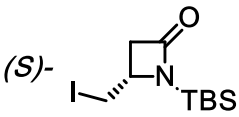
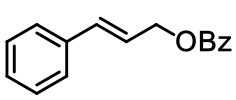
a palladium catalyst, or (c) is a potentially competitive coupling partner that could react with the boron reagent.

While Glorious' protocol utilized GC analysis relative to an internal standard to determine reaction conversion and yield, we found it of little trouble or consequence to simply isolate both reaction components. Thus, once the reaction was determined to be complete *via* TLC analysis, subsequent purification *via* silica gel chromatography allowed for isolated yields of *both* the desired butadiene product (**30**) as well as the additive molecule to be determined (Table 2).

Table 2. Robustness Screen as a Measure of Functional Group Tolerance/Compatibility

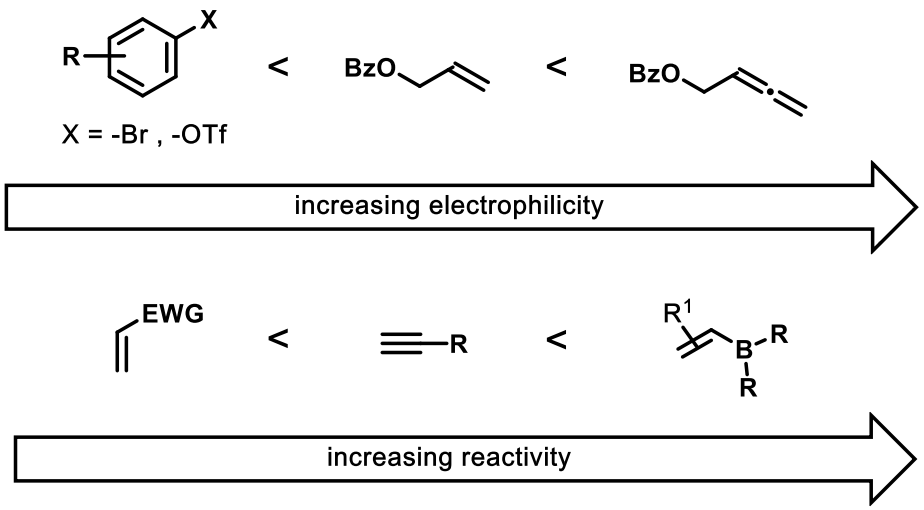


20 (1.00-1.05 equiv) → 30

entry	additive	additive recovered (%)	product 30 (%)
1	none	none	87
2		91	83
3		91	88
4		95	87
5		89	91
6		95	87
7		69	83
8		93	94
9		86	90
10		88	86

As shown in Table 2, each additive tested was recovered in high yield, and displayed no noticeable inhibitory effect on the desired transformation, consistently providing high yields of the desired diene. Competitive insertion by palladium into an (hetero)aryl bromide, aryl triflate or alkyl iodide was not observed (entries 2, 4, 8 and 9). Likewise, Michael acceptors, free amides, unprotected anilines, free indoles, and TBS-protected β-lactams remained untouched under these conditions. Only the highly functionalized *N*-propargylic amide (entry 7) was recovered in *relatively* low yield, albeit without affecting the efficiency of diene formation. Nonetheless, given all the possibilities for participation by this additive, such as oxidative addition, nitro reduction, directed *ortho*-C-H activation, Sonogashira-type insertion, acetylenic π-coordination, and so forth; an isolated additive recovery yield of 69% was still achieved. Most notable, however, is the exceedingly higher reactivity of π-allenyl intermediates, which was confirmed *via* entry 10, where the desired transformation of allenic benzoate **20** took place with complete selectivity over the analogous allylic benzoate. Alternatively, in the absence of the allenic benzoate educt (*i.e.* the analogous standard reaction with only the allylic benzoate from entry 10) the expected allylated product is quantitatively formed within 4-6 hours (not shown). Thus, the higher electrophilicity of π-allenyl systems, together with near stoichiometric amounts of coupling reagents, allowed for the excellent chemoselectivity observed, and highlighted, in this exemplary experiment.

Figure 5. Order of Reactivity in Pd-Catalyzed Cross-Couplings in Micellar Media



From analysis of the results described above, general reactivity patterns can be deduced. Thus, the order of reactivity associated with standard reagents used in micellar cross-coupling reactions can be summarized, as shown in Figure 5.

1.3. Conclusion

In conclusion, a mild and environmentally responsible methodology has been developed as a general strategy to access substituted 1,3-butadienes utilizing palladium catalysis under micellar reaction conditions. Compared to Suzuki's seminal procedure, reported in 1994, the technology described herein presents considerable improvements in terms of mildness, simplicity and generality. Other noteworthy advancements include the facile formation of new C-C bonds of any sp-sp^2, sp^2-sp^2 or sp^2-sp^3 nature exclusively at the 2-position of the resulting diene. Moreover, functional group tolerance as quantitatively and qualitatively demonstrated *via* robustness screening, regioselectivity, stereoselectivity and chemoselectivity appear to be exceptionally high. These developments have expanded the toolbox of technologies now available and further attest to the myriad of possibilities that lie ahead within the new world of organic synthesis in water.[11c,25]

1.4. References

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1.5. Experimental Data

1. General Experimental Details

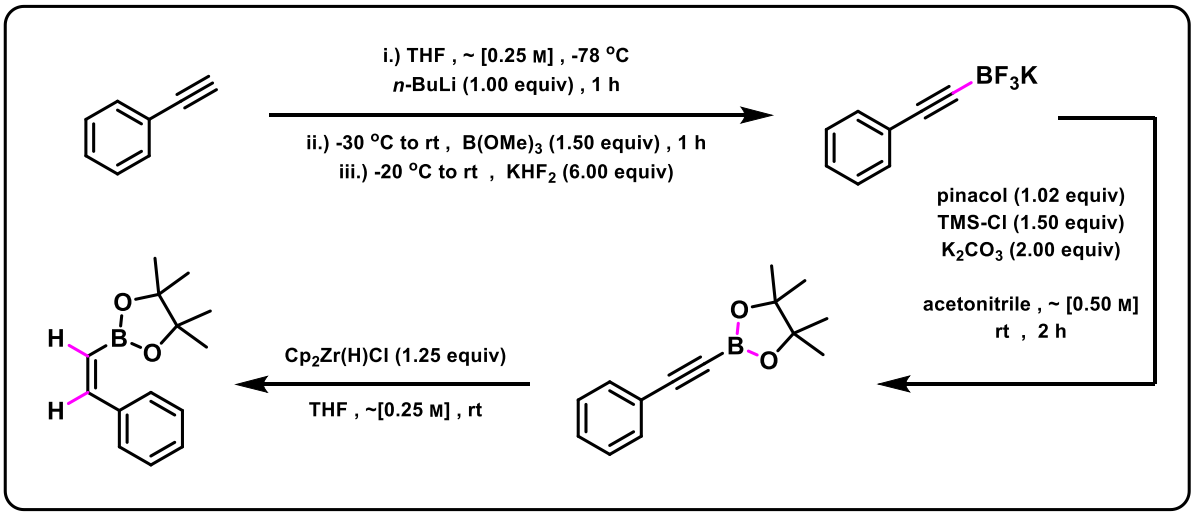
All manipulations were carried out under air unless otherwise noted. Silica gel TLC plates (standard grade, 230 – 400 mesh) were purchased from EMD Chemicals. Diethyl ether (Fisher), toluene (Aldrich), THF (Fisher) and DCM (Fisher) were purified using a solvent purifier system (SPS). Et_3N (Fisher) was dried over activated 4 Å molecular sieves and stored on dried 4 Å sieves under argon. NMR solvents were purchased from Cambridge Isotopes Laboratories. $CDCl_3$ was dried over activated 4 Å molecular sieves and then stored over dried 4 Å sieves. Reaction vials (4 mL with green top polypropylene cap and PTFE septa) were purchased from Chemglass Life Sciences, and used as received without further drying. Reaction vials (4 mL black top) were purchased from VWR, and used as received without further drying. Reaction vials were also recycled and re-used. A 2 wt % TPGS-750-M/H2O solution was prepared by dissolving 4 g TPGS-750-M in 196 g water (HPLC grade), followed by degassing with argon. TPGS-750-M was synthesized by a procedure published by this group,[1] and is also commercially available from Sigma-Aldrich (catalog #733857). Ligands and catalysts were generously received from F. Hoffmann-La Roche AG and Johnson Matthey. All other reagents were purchased from Aldrich and Fischer and used as received. Melting points were determined using a MEL-TEMP II melting point apparatus with samples in Kimble Kimex 51 capillaries (1.5-1.8 x 90 mm). IR spectra were acquired on a FTIR Perkin Elmer Spectrum Two: UATR Two spectrometer using 1 cm^{-1} resolution. High resolution mass analyses were obtained using a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies). As capillary column a HP-5MS cross-linked 5%

phenylmethylpolysiloxanediphenyl column (30 m x 0.250 mm, 0.25 micron, Agilent Technologies) was employed. Helium was used as carrier gas at a constant flow of 1 mL/min. Elemental analyses were performed at UCSB.

Unless otherwise noted, all reactions were performed under argon, except for the oxidative cleavage reactions, which were run open to air. Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F_{254} plates (Merck, 0.25 mm thick). Developed chromatograms were analyzed by UV (lamp, 254 nm). Non-UV active compounds were developed using aqueous potassium permanganate ($KMnO_4$), Vanillin/H_2SO_4, Ceric Ammonium Molybdenate (CAM stain), or Seebach's stain. Flash chromatography was performed in glass columns using Silica Flassh® P60 (SiliCycle, 40-63 μm). GCMS data was recorded on a 5975C Mass Selective Detector coupled with a 7890A Gas Chromatograph (Agilent Technologies). A capillary column (HP-5MS cross- linked 5% phenylmethylpolysiloxanediphenyl, 30 m x 0.250 mm, 0.25 micron, Agilent Technologies) was employed. Helium was used as carrier gas at a constant flow of 1 mL/min. NMR analyses were recorded at 22 °C on a Varian UNITY INOVA Avance at 400, 500, or 600 MHz. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the scale from an internal standard of residual chloroform (7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sex = sextet, sep = septet, m = multiplet, br = broad w = weak), coupling constant in Hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.16 ppm) on the δ scale.

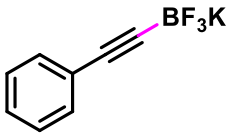
2. Synthetic Details

2.1 Synthesis of coupling partners



Trifluoro(phenylethynyl)-λ^4-borane, potassium salt [3]

Notebook: DJL-4-115



To a solution of phenylacetylene in THF, ~[0.25 M], (10.00 mmol, 1.00 equiv), was added *n*-butyllithium (1.00 equiv) dropwise at -78 °C, and the resulting solution was stirred for 1 h. The cold bath was then adjusted to -30 °C and trimethylborate (1.50 equiv) was introduced dropwise, the solution was allowed to stir at this temperature for 1 h, then for an additional hour at rt. The reaction was then quenched, at 0 °C with vigorous stirring, by addition of an aqueous solution of KHF_2, [5.0 M], and further stirred for an additional 2-4 h (extra time stirring has no adverse effect) at rt (open flask). All solvent was removed *via* rotary evaporation (with aid of a heat gun if necessary), the resulting white residue was azeotroped with acetone

to aid in removal of trace water (x 2-3). The RBF containing the crude white residue was then filled ~½ full with acetone and heated with rotation on the roto-vap, without vacuum (just below the boiling point of acetone) for ~10-15 min (inorganic salts will remain suspended), and directly filtered 'hot' *via* vacuum filtration. This process was repeated on the RBF retaining the inorganic salts once more. The collected acetone washes were concentrated and once more heated and filtered to afford a white crystalline solid, which was triturated with pentanes (x 2-3), and stored under high vacuum to afford the desired compound as a white crystalline solid, 1.202 g, 58%.

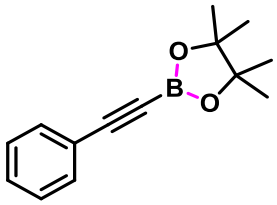
***Note:** Product $-BF_3K$ salt is soluble in hot acetone, whereas excess KHF_2 is not.

^{1}H NMR: (500 MHz, acetone-d_6) δ 7.38 – 7.29 (m, 2H), 7.27 – 7.17 (m, 3H)

^{13}C NMR: (126 MHz, acetone) δ 132.1, 132.1, 128.8, 128.8, 127.3, 99.4

4,4,5,5-Tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane [4]

Notebook: DJL-6-264



To a RBF, containing a Teflon coated stir bar, were dissolved the acetylinic-BF_3K salt (1.90 mmol, 1.00 equiv), K_2CO_3 (2.00 equiv) and pinacol (1.02 equiv) in acetonitrile at [0.50 M]. The resulting mixture was stirred at rt followed by the dropwise addition of TMS-Cl (1.50 equiv), upon complete addition the solution was further stirred for ~2-3 h. The reaction was then diluted with ether (~1/2 the reaction volume), stirred for 5 min and allowed to settle. The salts were removed *via* filtration, and the crude organics removed *in vacuo*. The resulting crude

residue was immediately purified *via* column chromatography on silica gel, eluting with 75% (EtOAc : hexanes), to afford the desired compound as a white solid, 268 mg, 62%.

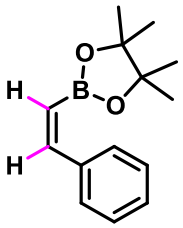
*Note: Purification of boronate esters should be performed immediately after reaction work-up, and chromatography should take no longer than 10 min.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.56 – 7.47 (m, 2H), 7.38 – 7.29 (m, 3H), 1.32 (s, 12H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 132.7, 132.3, 129.5, 128.9, 128.4, 128.4, 122.0, 84.6, 77.3, 24.9

(*Z*)-4,4,5,5-Tetramethyl-2-styryl-1,3,2-dioxaborolane [5]

Notebook: DJL-6-268



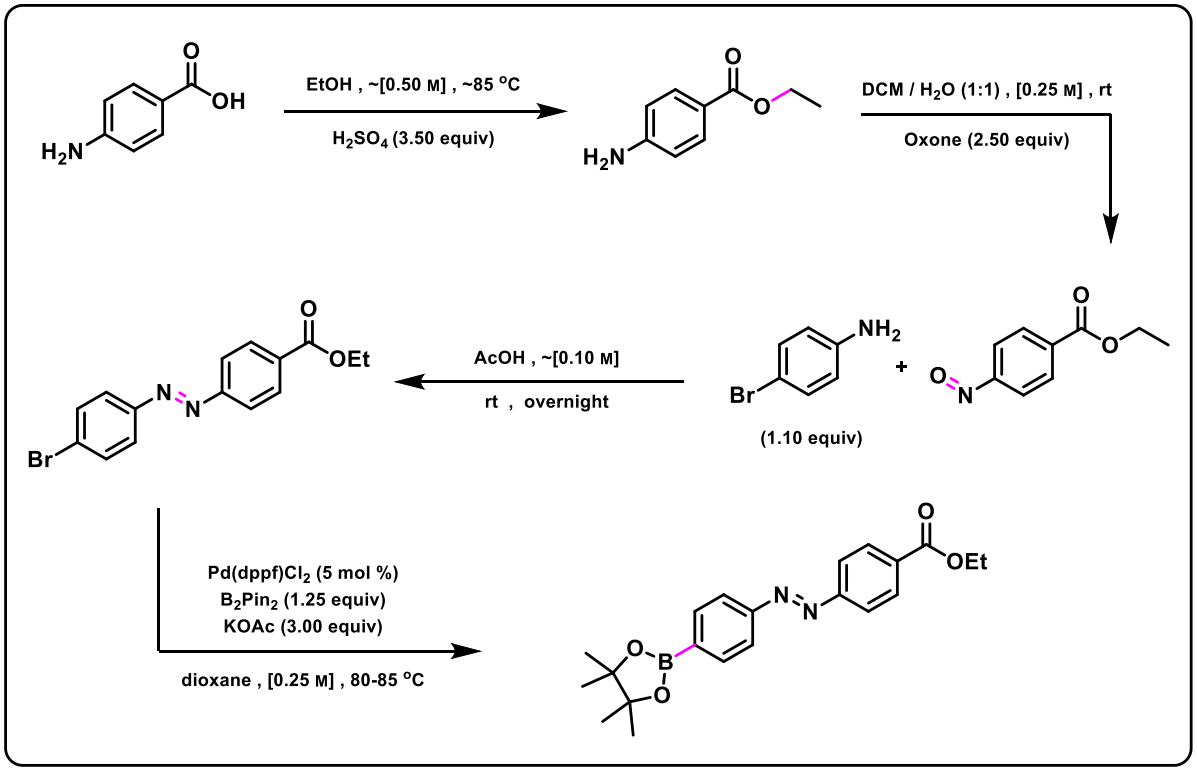
Schwartz's reagent (1.25 equiv) was weighed into a RBF containing a stir bar, the flask was placed under an argon atmosphere, to which was then added dry THF to arrive at a [0.50 M] mixture, all at rt. To this stirred suspension was added dropwise a solution of the acetylenic boronate pinacol ester (0.75 mmol, 1.00 equiv) in THF [0.50 M]. The reaction was stirred overnight at rt, producing a clear, green-yellow solution. Upon completion, as judged *via* TLC analysis, the reaction was quenched with water and transferred to a separatory funnel with ether. The aqueous phase was extracted (x 3) with ether and the collected organic layers were dried over anhydrous Na_2SO_4. The crude organic layers were then passed through a plug of silica with EtOAc to afford the desired compound as a pale yellow solid, without need for further purification, 144 mg, 84%.

TLC: R_f = 0.68 (75% EtOAc : hexanes), UV, I_2, $KMnO_4$

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 2H), 7.32 – 7.25 (m, 4H), 5.60 (d, *J* = 14.9 Hz, 1H), 1.29 (s, 12H)

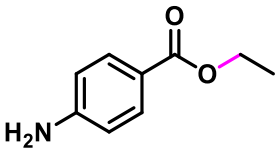
^{13}C NMR: (126 MHz, $CDCl_3$) δ 148.3, 128.8, 128.1, 128.1, 103.9, 83.6, 24.9

IR: 2984, 2927, 2854, 1617, 1451, 1331, 1258, 1139 cm^{-1}



Ethyl 4-aminobenzoate (Benzocaine)

Notebook: DJL-7-035



To a stirred solution of 4-aminobenzoic acid (50.00 mmol, 1.00 equiv) in absolute ethanol, [0.50 M], was added dropwise concentrated sulfuric acid (3.50 equiv). The RBF was

fitted with a jacketed water condenser and submerged in an oil bath, and the mixture was allowed to stir at reflux (bath set to ~85 ^{o}C) overnight. Once the reaction was complete, *via* TLC analysis, the oil bath was removed and the RBF was allowed to cool to rt. Removal of the stir bar and concentration of the reaction mixture to ¼ its volume *in vacuo* afforded a crude viscous material which was transferred to a large Erlenmeyer flask, containing a stir bar, with water and minimal ether. The flask was cooled in an ice bath and carefully quenched with aqueous Na_2CO_3, with stirring, until a neutral pH was reached. The contents were then transferred to a separatory funnel and the aqueous phase was extracted with ether (x 3), the organic extracts were concentrated to 1/3 their volume and washed with $NaHCO_3$ (x 2-3) (to remove any trace carboxylic acid). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*, to afford the desired compound as clear/ faintly beige crystals, 6.772 g, 82%, without need for further purification.

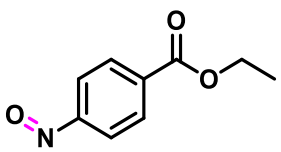
***Note:** 3.50 equivalents of acid is required to deactivate the aniline moiety; use of fewer equivalents resulted in poor conversions, and catalytic amounts resulted in little to no reaction.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.06 – 7.65 (m, 2H), 6.67 – 6.60 (m, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.03 (bs, 2H), 1.36 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 166.9, 150.9, 131.7, 120.2, 113.9, 60.4, 14.6

Ethyl 4-nitrosobenzoate [6]

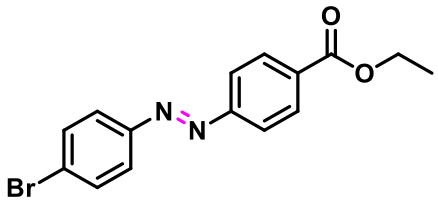
Notebook: DJL-7-030-A/039-A-step-I



To an Erlenmeyer flask (with good head space available), containing a Teflon coated stir bar, the starting aniline (15.00 mmol, 1.00 equiv) was dissolved in DCM, ~[0.25 M], at rt with vigorous stirring. To the stirred mixture was slowly added, portion-wise, an aqueous solution of Oxone® (2.50 equiv, [0.25 M]), and the reaction was allowed to proceed for 3 h to overnight, during which time a significant color change was observed. Upon complete consumption of aniline, *via* TLC analysis, the mixture was transferred to a separatory funnel. The aqueous phase was extracted with DCM (x 2-3), concentrated to ½ its volume and then further washed with DI water (x 2-3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to ~10% its initial volume. This material was directly used in the subsequent step without further manipulation.

Ethyl (*E*)-4-((4-bromophenyl)diazenyl)benzoate

Notebook: DJL-7-039-A-step-II



The nitroso ethyl ester above (15.00 mmol, 1.00 equiv), formed *in situ*, was taken up in glacial acetic acid to reach [0.10 M], followed by the addition of 4-bromoaniline (1.10 equiv). The reaction mixture was allowed to stir at rt overnight (~12 h). The reaction was diluted with water and transferred to an Erlenmeyer flask and *very slowly* neutralized with saturated aqueous $NaHCO_3$, with stirring. The aqueous layer was extracted with DCM (x 2), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was subsequently purified *via* column chromatography on silica gel, eluting with 5% then 10%

(ether : hexanes), to afford the desired compound as a free-flowing vibrant deep tangerine solid, 1.942 g, 39%.

TLC: R_f = 0.54 (20% ether : hexanes), UV, self stains on TLC plate

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.21 – 8.17 (m, 2H), 7.98 – 7.91 (m, 2H), 7.86 – 7.79 (m, 2H), 7.71 – 7.63 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 166.1, 155.0, 151.4, 132.6, 130.8, 126.4, 124.7, 122.8, 61.5, 14.5

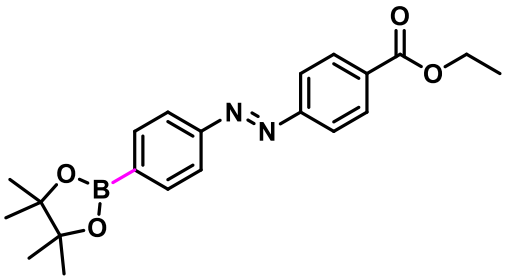
IR: 2922, 2854, 1716, 1274, 1102 cm^{-1}

HRMS: (ESI) calculated for $[C_{15}H_{13}BrN_2O_2]$: 333.0239 $[M+H]^+$, found 333.0224

*Predominately the *trans*-isomer

Ethyl (*E*)-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)diazenyl)benzoate

Notebook: DJL-7-046



A clean and dry RBF was taken into a glove box and charged with $Pd(dppf)Cl_2$ (5 mol %), B_2Pin_2 (1.25 equiv) and KOAc (3.00 equiv). Outside the glove box 'wet' dioxane (not freshly distilled, trace moisture being advantageous for palladium catalyzed cross-couplings) was added to the flask ~[0.25 M], with stirring, followed by the corresponding aryl bromide (2.00 mmol, 1.00 equiv). The flask was then fitted with a Vigreux air condenser and stirred at 80 ^{o}C for 2 h under argon. After cooling to rt, TLC analysis had indicated complete

consumption of starting aryl bromide. The reaction flask was then transferred to a separatory funnel with ether and water, and the aqueous phase was extracted with ether (x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was directly purified *via* column chromatography on silica gel, eluting with 20% (ether : hexanes), to afford the desired compound as a free-flowing deep orange/red solid, 514 mg, 68%.

TLC: R_f = 0.33 (20% ether : hexanes), UV, self stains on TLC plate

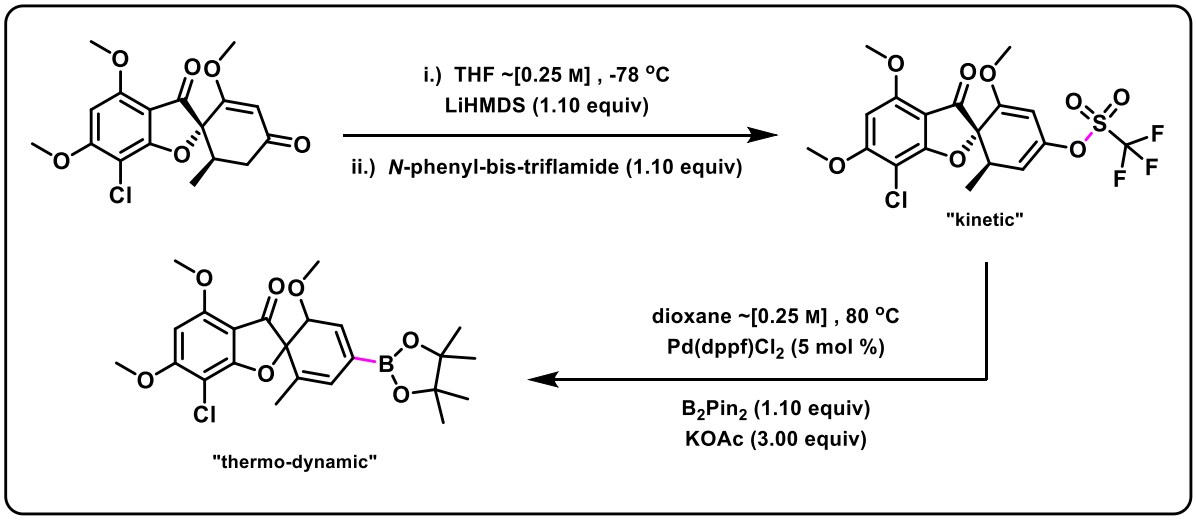
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.23 – 8.18 (m, 2H), 8.01 – 7.94 (m, 4H), 7.95 – 7.89 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.38 (s, 12H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 166.2, 155.3, 154.4, 135.8, 132.5, 130.7, 122.8, 122.4, 84.3, 61.4, 25.1, 14.5

IR: 2984, 2922, 2849, 1721, 1357, 1269 cm^{-1}

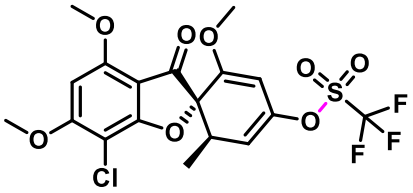
HRMS: (ESI) calculated for $[C_{21}H_{25}BN_2O_4]$: 381.1989 $[M+H]^+$, found 381.1992

*Predominately the *trans*-isomer



(2*S*,6'*R*)-7-Chloro-2',4,6-trimethoxy-6'-methyl-3-oxo-3*H*-spiro[benzofuran-2,1'-cyclohexane]-2',4'-dien-4'-yl trifluoromethanesulfonate [2]

Notebook: DJL-6-224



To a clean and dry RBF charged with a stir bar and containing the corresponding ketone (7.00 mmol, 1.00 equiv), in dry THF, ~[0.25 M], at -78 °C, was added LiHMDS (1.10 equiv) in one portion as a solid. Stirring was continued at this temperature for 2 h at which point *N*-phenyl-bis-triflamide (1.10 equiv) was introduced in one portion as a solid. The reaction mixture was allowed to warm to rt over the course of ~12 h at which point TLC analysis indicated completion. The reaction was then quenched with saturated aqueous ammonium chloride and extracted with ether (x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was subsequently

purified *via* column chromatography on silica gel, eluting with 50% then 60% (EtOAc : hexanes), to afford the desired compound as a white solid, 1.592 g, 47%.

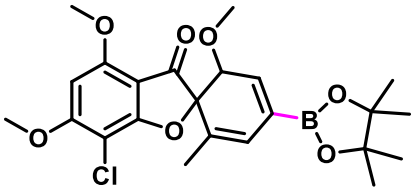
TLC: R_f = 0.17 (40% EtOAc : hexanes), UV, I_2, vanillin stain (purple that fades to olive green spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.10 (s, 1H), 5.40 (dd, *J* = 4.0, 1.9 Hz, 1H), 5.19 (d, *J* = 1.9 Hz, 1H), 3.99 (s, 3H), 3.95 (s, 3H), 3.58 (s, 3H), 3.23 (qd, *J* = 7.3, 4.0 Hz, 1H), 1.13 (d, *J* = 7.3 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 192.0, 191.9, 168.8, 164.4, 157.9, 157.9, 156.9, 143.9, 112.0, 117.4, 105.1, 105.1, 97.4, 95.6, 94.3, 90.2, 88.9, 58.8, 58.2, 58.2, 57.6, 57.0, 57.0, 56.5, 55.9, 55.8, 55.3, 54.7, 38.3, 37.2

7-Chloro-4,6,6'-trimethoxy-2'-methyl-4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3*H*-spiro[benzofuran-2,1'-cyclohexane]-2',4'-dien-3-one

Notebook: DJL-6-225



A clean and dry RBF was taken into a glove box and charged with Pd(dppf)Cl_2 (5 mol %), B_2Pin_2 (1.10 equiv) and KOAc (3.00 equiv). Outside the glove box 'wet' dioxane (not freshly distilled, trace moisture being advantageous for palladium catalyzed cross-couplings) was added to the flask, ~[0.25 M], with stirring, followed by the corresponding vinyl triflate (3.00 mmol, 1.00 equiv). The flask was then fitted with a Vigreux air condenser and stirred at 80 ^{o}C for 2 h under argon. After cooling to rt, TLC analysis had indicated complete

consumption of starting vinyl triflate. The reaction flask was then transferred to a separatory funnel with ether and DI water, and the aqueous phase was extracted with ether (x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was directly purified *via* column chromatography on silica gel, eluting with 50% (EtOAc : hexanes), to afford the desired compound as an off-white solid, 374 mg, 27%.

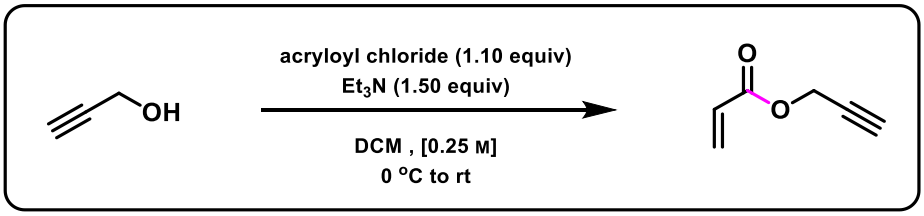
TLC: R_f = 0.45 (50% EtOAc : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.27 (s, 1H), 7.14 (s, 1H), 5.91 (s, 1H), 3.95 (s, 3H), 3.75 (s, 3H), 3.68-3.39 (s split, 1H), 3.40 (s, 3H), 2.13 (s, 3H), 1.37 (s, 12H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 200.2, 162.1, 161.8, 140.7, 136.7, 133.4, 129.1, 129.1, 129.0, 113.5, 87.1, 83.9, 56.3, 56.0, 55.9, 24.9, 18.5

IR: 2974, 2927, 2849, 1607, 1581, 1367, 1274, 1128, 1097 cm^{-1}

HRMS: (ESI) calculated for [$C_{23}H_{28}BClO_7$]: 463.1699 $[M+H]^+$, found 463.1712



Prop-2-yn-1-yl acrylate (19)

Notebook: DJL-5-211

To a solution of propargyl alcohol (20.00 mmol, 1.00 equiv) in DCM, [0.25 M], at 0 °C was added triethylamine (1.50 equiv), and the mixture was stirred ~5-10 min. Then, acryloyl chloride (1.10 equiv) was introduced dropwise (with a wide gauge vent-needle), and the reaction was allowed to slowly warm to rt (~2-12 h). Once TLC analysis had indicated full conversion the reaction was quenched with saturated aqueous $NaHCO_3$ and transferred to a separatory funnel with DI water and DCM. The organic phase was washed with 10% aqueous HCl (x 3), then saturated aqueous $NaHCO_3$, then DI water, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. To the crude material were added a few crystals of MEHQ (radical inhibitor) and was of acceptable purity to use as such; clear light-yellow oil, 1.705 g, 77%.

TLC: R_f = 0.21 (10% ether : hexanes), UV, I_2

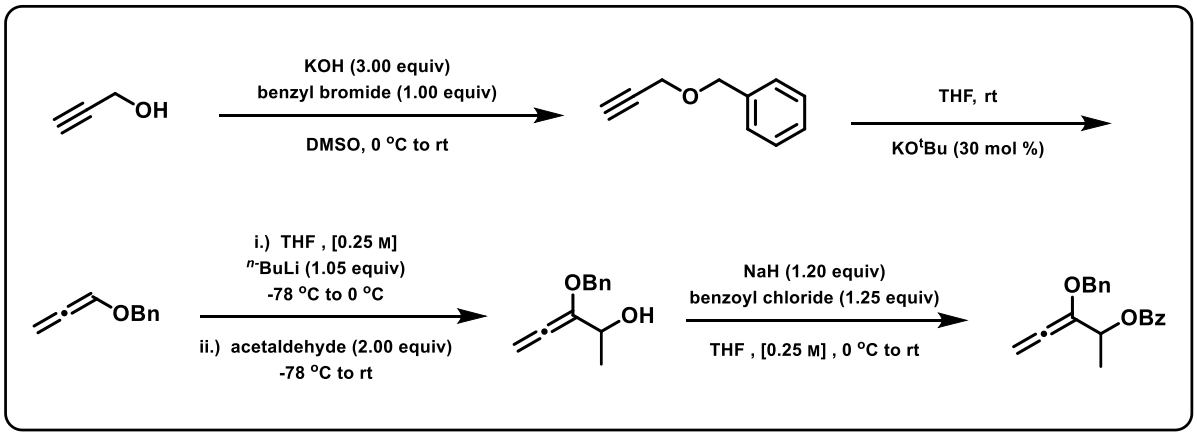
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.46 (d, *J* = 17.5 Hz, 1H), 6.14 (ddd, *J* = 17.4, 10.5, 0.7 Hz, 1H), 5.88 (d, *J* = 10.5, Hz, 1H), 4.75 (d, *J* = 2.5 Hz, 2H), 2.48 (t, *J* = 2.5 Hz, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 165.4, 132.0, 127.7, 77.7, 75.1, 52.2

IR: 3285, 2126, 1726, 1409, 1170 cm^{-1}

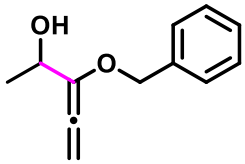
2.2 Synthesis of allenic esters [2,7]

All allenic esters, and their intermediates, were prepared according to literature procedures. Only the allenoate shown below was unknown.



3-(Benzyloxy)penta-3,4-dien-2-ol

Notebook: DJL-5-032



To a RBF charged with a magnetic stir bar and dry THF was added allenyl benzyl ether (20.00 mmol, 1.00 equiv, prepared according to known literature procedures, see reference section) and the resulting solution, ~[0.25 M], was cooled to -78 °C with stirring. Once at -78 °C, *n*-BuLi (~[2.25 M] in hexanes; 1.05 equiv) was added dropwise, and this mixture was then stirred for ~30-45 min at -78 °C and then ~30 min at rt. After this time, the solution was again brought to -78 °C and acetaldehyde (2.00 equiv) was added dropwise, as a concentrated solution in THF at 0 °C, the reaction mixture was covered with aluminum foil and allowed to stir overnight (~8-12 h). Once the reaction was complete *via* TLC analysis (see below) the reaction was quenched with saturated aqueous ammonium chloride, followed by transfer to a separatory funnel with DI water and diethyl ether. Extraction with ether (x 3) followed by

drying of the organic extracts with anhydrous Na_2SO_4, filtration, and subsequent concentration *via* rotary evaporation provided the crude material which was then subjected to column chromatography on silica gel, eluting with 10% then 20% (ether : hexanes), to obtain the title compound as a clear colorless oil or as a light pale yellow viscous oil, 2.805 g, 74%.

***Note:** The reagent bottle of acetaldehyde (very low boiling point) was placed in an ice bath, fitted with a rubber septum, and the desired amount was transferred to a separate, pre-cooled (*via* ice bath) RBF (under argon) and dissolved in dry THF, ~[1.00 M]. This solution was transferred while cold to the reaction.

***Note:** The flash column should be packed and run with 1-2% Et_3N to avoid acid-mediated decomposition of the cumulated enol ether.

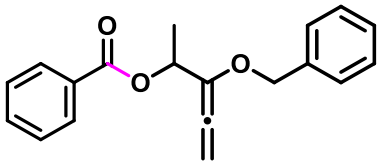
TLC: R_f = 0.31 (20% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.55 (d, *J* = 2.1 Hz, 2H), 4.65 (s, 2H), 4.42 (m, 1H), 2.43 – 2.08 (bs, 1H), 1.34 (d, *J* = 6.5 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 196.7, 137.4, 135.9, 128.5, 128.0, 127.7, 92.7, 70.9, 66.9, 20.5

3-(Benzyloxy)penta-3,4-dien-2-yl benzoate

Notebook: DJL-5-034



To a slurry of NaH (1.20 equiv) in THF, at [0.25 M] global concentration, at 0 ^oC was added dropwise (with a vent needle) a concentrated solution of the corresponding allenol (5.786 mmol, 1.00 equiv) in THF. The mixture was stirred for 45-60 min and a concentrated

solution of benzoyl chloride, in THF, was introduced slowly. The resulting mixture was allowed to stir, thus 0 ^{o}C to rt, overnight. The reaction was diluted with ether at 0 ^{o}C followed by slow dropwise addition of water, until no more gas evolved (to quench any residual NaH) and transferred to a separatory funnel. Extraction with ether (x 3) followed by drying of the organic extracts with anhydrous Na_2SO_4, filtration, and subsequent concentration *via* rotary evaporation provided the crude material which was then subjected to column chromatography on silica gel, eluting with 1 then 2% then 3% (ether : hexanes), to obtain the title compound as a clear colorless oil or as a light pale yellow viscous oil, 603 mg, 35%.

***Note:** The flash column should be packed and run with 1-2% Et_3N to avoid acid-mediated decomposition of the cumulated enol ether.

TLC: R_f = 0.42 (10% ether : hexanes), UV, I_2

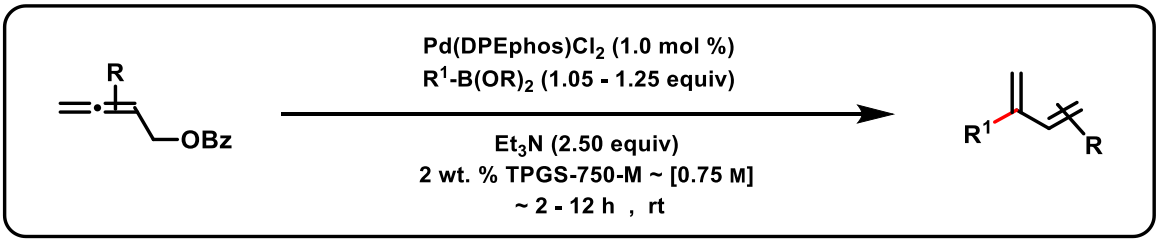
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.58 – 7.54 (m, 1H), 7.44 (m, 2H), 7.41 – 7.22 (m, 5H), 5.77 (m, 1H), 5.56 (m, 2H), 4.70 (s, 2H), 1.53 (d, J = 6.6 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 198.3, 166.0, 137.6, 133.0, 133.0, 130.7, 129.9, 128.4, 128.4, 127.8, 127.6, 92.5, 70.7, 69.8, 18.1

3. General Methods for Diene Synthesis

3.1 General procedure 'A'

Suzuki-Miyaura and Sonogashira mediated sp^2-sp^2 and sp-sp^2 cross-couplings



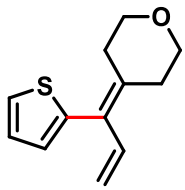
Into a screw cap vial was measured the desired allenic ester (1.00 equiv) followed by Pd(DPEphos)Cl_2 (≤1 mol %). To this vial was then added a 2 wt % solution of TPGS-750-M in DI water to arrive at a ~[0.75 M] solution and the reaction mixture was stirred with a strong vortex at rt. Then 'a few drops' of Et_3N were added (to aid in reaction homogeneity, and possibly facilitating initial reduction of the Pd(II) catalyst to the active Pd(0) species) followed by addition of the boron coupling partner (1.05 – 1.25 equiv) either dropwise for oils or in one portion for solids, followed by the remainder of Et_3N (2.50 equivalents total) while rinsing any residue from the wall of the vial into solution. The reaction was capped and allowed to stir at rt for ~ 2–12 h. Upon complete consumption of allenic ester *via* TLC analysis (see below) a small amount of EtOAc was added to the reaction and the mixture was gently stirred for ~ 5–10 min (milky pale yellow/orange solution will eventually become clear yellow/orange). This mixture was directly passed through a short plug of Celite on top of silica gel with ether and

concentrated *via* rotary evaporation. Purification by column chromatography on silica gel afforded the desired product.

***Note:** The allenic ester is usually added first *via* glass pipette capillary action. This is due to the highly viscous nature of most of the allenic esters utilized in this research. Use of a microliter syringe was overly cumbersome, as well use of a disposable syringe/needle was impractical due to substantial, yet unavoidable, transfer losses of valuable material. However, reactions are typically unaffected by the order of addition as long as the boronate coupling partner is added last to help avoid potential protodeborylation.

4-(1-(Thiophen-2-yl)allylidene)tetrahydro-2*H*-pyran (1)

Notebook: DJL-6-194-B



Purification: column chromatography on silica gel eluting with 10% (ether : hexanes), clear colorless oil, (0.50 mmol scale) 83.3 mg, 81%.

TLC: R_f = 0.29 (10% ether : hexanes), UV, I_2, vanillin stain (olive/ grey spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.02 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.93 (dd, *J* = 16.9, 10.6 Hz, 1H), 6.76 (dd, *J* = 3.4, 1.0 Hz, 1H), 5.15 (dd, *J* = 10.6, 1.4 Hz, 1H), 4.88 (dd, *J* = 16.9, 1.3 Hz, 1H), 3.80 – 3.74 (m, 2H), 3.64 (t, *J* = 5.5 Hz, 2H), 2.64 – 2.57 (m, 2H), 2.24 (t, *J* = 5.5 Hz, 2H)

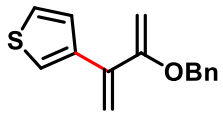
^{13}C NMR: (126 MHz, $CDCl_3$) δ 139.8, 139.5, 134.3, 127.3, 126.9, 125.3, 117.1, 99.2, 69.1, 68.7, 33.8, 31.3

IR: 3088, 2958, 2838, 1622, 1232, 1097, 692 cm^{-1}

HRMS: (ESI) calculated for $[C_{12}H_{14}OS]$: 207.0844 $[M+H]^+$, found 207.0837

3-(3-(Benzyloxy)buta-1,3-dien-2-yl)thiophene (2)

Notebook: DJL-7-262-A



Purification: column chromatography on silica gel eluting with 2% (ether : hexanes), white solid, (0.30 mmol scale) 64.4 mg, 89%.

TLC: R_f = 0.69 (30% ether : hexanes), UV, I_2, vanillin stain (deep blue/ grey spot)

^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.48 – 7.38 (m, 4H), 7.38 – 7.27 (m, 3H), 7.23 – 7.13 (m, 1H), 5.74 (d, *J* = 1.8 Hz, 1H), 5.37 (s, 1H), 4.93 (s, 2H), 4.41 (s, 2H)

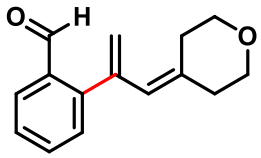
^{13}C NMR: (151 MHz, $CDCl_3$) δ 159.9, 140.8, 140.3, 137.2, 128.6, 128.2, 127.9, 127.5, 126.5, 126.2, 124.9, 123.2, 119.9, 115.0, 87.9, 69.8

IR: 3108, 3062, 2911, 1581, 1217, 1180, 697 cm^{-1}

HRMS: (ESI) calculated for $[C_{15}H_{14}OS]$: 243.0844 $[M+H]^+$, found 243.0838

2-(3-(Tetrahydro-4*H*-pyran-4-ylidene)prop-1-en-2-yl)benzaldehyde (3)

Notebook: DJL-5-145



Purification: column chromatography on silica gel eluting with 30% (ether : hexanes), clear colorless oil, (0.40 mmol scale) 80.4 mg, 88%.

TLC: R_f = 0.35 (40% ether : hexanes), UV, I_2, vanillin stain (blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ (10.19, 9.87 – 9.80 (s, H)), (8.06 - 7.91 (m, 1H)), (7.67 - 7.53 (m, 1H)), (7.45 – 7.38 (m, 1H)), (7.33 - 7.6, (m, 1H)), 6.13 (s, 1H), 5.47 (s, 1H), 5.13 (d, *J* = 2.0 Hz, 1H), 3.80 – 3.67 (t, *J* = 5.5 Hz, 2H), 3.49 – 3.42 (t, *J* = 5.5 Hz, 2H), 2.28 (dt, *J* = 10.8, 2.9 Hz, 2H), 1.98 – 1.94 (dt, *J* = 10.8, 2.9 Hz, 2H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 192.2, 146.4, 142.6, 139.7, 133.9, 133.8, 129.7, 128.0, 127.6, 125.7, 121.5, 69.4, 68.2, 37.9, 31.0

IR: 2958, 2849, 2745, 1690, 1596, 1097, 1009, 754 cm^{-1}

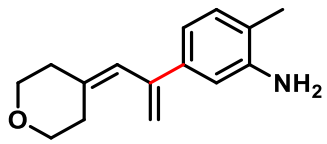
HRMS: (ESI) calculated for [$C_{15}H_{16}O_2$]: 251.1048 $[M+Na]^+$, found 251.1051

***Note:** Rotamers of *s-cis* and *s-trans* diene moieties observed with bulky, yet flexible or having the ability to coordinate, -*ortho* aromatic groups.

~ 4:1 ratio of restricted rotamers (see Spectra section)

2-Methyl-5-(3-(tetrahydro-4*H*-pyran-4-ylidene)prop-1-en-2-yl)aniline (4)

Notebook: MRM-1-062



Purification: column chromatography on silica gel eluting with 40% (ether : hexanes), pale yellow solid, (0.40 mmol scale) 77.0 mg, 84%.

TLC: R_f = 0.23 (50% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.0 Hz, 1H), 6.78 (dd, *J* = 7.75, 1.75 Hz, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 5.98 (d, *J* = 1.0 Hz, 1H), 5.46 (d, *J* = 1.5 Hz, 1H), 5.00 (t, *J* = 1.5 Hz, 1H), 3.79 – 3.76 (m, 2H), 3.62 (m, 4H), 2.36 (m, 4H), 2.17 (s, 3H)

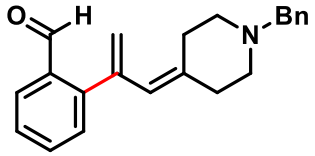
^{13}C NMR: (126 MHz, $CDCl_3$) δ 144.5, 144.4, 139.9, 138.9, 130.5, 124.1, 122.1, 117.2, 114.0, 113.2, 69.8, 69.1, 37.4, 31.3, 17.3

IR: 3452, 3363, 2963, 2854, 1565, 1092, 900 cm^{-1}

HRMS: (ESI) calculated for [$C_{15}H_{19}NO$]: 230.1545 $[M+H]^+$, found 230.1553

2-(3-(1-Benzylpiperidin-4-ylidene)prop-1-en-2-yl)benzaldehyde (5)

Notebook: DJL-4-234



Purification: column chromatography on silica gel eluting with 40% (ether : hexanes), off-yellow solid, (0.30 mmol scale) 68.8 mg, 72%.

TLC: R_f = 0.26 (40% ether : hexanes), UV, I_2, vanillin stain (orange/ tangerine spot)

^{1}H NMR: (500 MHz, $CDCl_3$): δ 10.17 (s, 1H), 7.88 (m, 1H), 7.56 – 7.26 (m, 7H), 7.23 – 7.19 (m, 1H), 6.06 (s, 1H), 5.43 (s, 1H), 5.08 (d, *J* = 2.0 Hz, 1H), 3.43 (s, 2H), 2.49 – 2.44 (t, *J* = 5.75 Hz, 2H), 2.29 – 2.26 (t, *J* = 5.50 Hz, 2H), 2.20 (t, *J* = 5.50 Hz, 2H), 1.95 (t, *J* = 5.50 Hz, 2H)

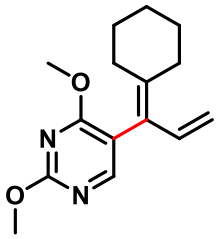
^{13}C NMR: (126 MHz, $CDCl_3$) δ 192.4, 146.7, 143.0, 141.9, 138.6, 133.9, 133.7, 129.8, 129.1, 128.3, 127.8, 127.4, 127.1, 125.1, 121.2, 62.9, 55.2, 54.0, 37.1, 29.5

IR: 3031, 2932, 2797, 2750, 1690, 1596, 1269, 733 cm^{-1}

HRMS: (ESI) calculated for [$C_{22}H_{23}NO$]: 318.1858 $[M+H]^+$, found 318.1856

4-(1-Cyclohexylideneallyl)-2,6-dimethoxypyrimidine (6)

Notebook: DJL-5-017



Purification: column chromatography on silica gel loaded with minimal DCM and eluting with 10%, then 20%, then 30% (ether : hexanes), clear colorless oil, (0.50 mmol scale) 100.6 mg, 77%.

TLC: R_f = 0.38 (20% ether : hexanes), UV, I_2, vanillin stain (orange/ maroon spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 6.96 (dd, *J* = 17.25, 10.75 Hz, 1H), 4.96 (dd, *J* = 10.75, 1.25 Hz, 1H), 4.53 (dd, *J* = 17.0, 1.50 Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 2.52 – 2.39 (m, 2H), 1.93 – 1.84 (m, 2H), 1.68 – 1.40 (m, 6H)

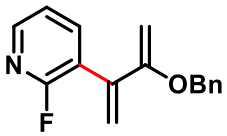
^{13}C NMR: (126 MHz, $CDCl_3$) δ 169.2, 164.7, 159.1, 145.0, 133.9, 123.4, 114.5, 113.7, 54.8, 54.0, 33.4, 30.3, 28.3, 28.2, 26.8

IR: 2922, 2849, 1591, 1555, 1461, 1388 cm^{-1}

HRMS: (ESI) calculated for [$C_{15}H_{20}N_2O_2$]: 261.1603 $[M+H]^+$, found 261.1600

3-(3-(Benzyloxy)buta-1,3-dien-2-yl)-2-fluoropyridine (7)

Notebook: DJL-7-262-B



Purification: column chromatography on silica gel eluting with 5% (ether : hexanes), clear colorless oil, (0.30 mmol scale) 64.2 mg, 84%.

TLC: R_f = 0.39 (30% ether : hexanes), UV, I_2, vanillin stain (teal spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.30 – 8.07 (m, 1H), 7.70 (m, 1H), 7.55 – 7.29 (m, 5H), 7.22 – 7.13 (m, 1H), 6.01 (d, *J* = 1.0 Hz, 1H), 5.31 (s, 1H), 4.90 (s, 2H), 4.37 (d, *J* = 2.0 Hz, 1H), 4.06 (d, *J* = 3.0 Hz, 1H)

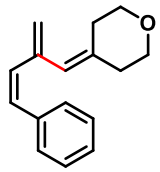
^{13}C NMR: (126 MHz, $CDCl_3$) δ 161.8, 159.9, 158.5, 147.0, 146.9, 141.9, 141.8, 138.3, 138.3, 137.0, 128.6, 128.0, 127.5, 122.8, 122.6, 121.3, 121.2, 118.5, 118.5, 87.9, 70.0

IR: 3067, 3031, 2911, 2864, 1726, 1601, 1430, 1248, 1191, 697 cm^{-1}

HRMS: (ESI) calculated for [$C_{16}H_{14}FNO$]: 256.1138 $[M+H]^+$, found 256.1142

(*Z*)-4-(2-Methylene-4-phenylbut-3-en-1-ylidene)tetrahydro-2*H*-pyran (8)

Notebook: DJL-6-270



Purification: column chromatography on silica gel eluting with 12% (ether : hexanes), light golden solid, (0.347 mmol scale) 55.8 mg, 71%.

TLC: R_f = 0.40 (20% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.43 – 7.05 (m, 5H), 6.47 (d, *J* = 12.0 Hz, 1H), 6.26 (d, *J* = 12.0 Hz, 1H), 5.64 (s, 1H), 5.19 (s, 1H), 5.03 (s, 1H), 3.58 (m, 4H), 2.51 – 2.47 (m, 2H), 2.07 – 2.04 (m, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 142.2, 137.5, 137.1, 131.9, 130.2, 129.3, 127.8, 127.0, 124.3, 119.4, 69.2, 68.4, 37.3, 31.2

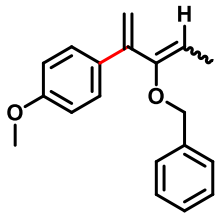
IR: 2953, 2927, 2849, 1716, 1456, 1232, 1102, 993, 697 cm^{-1}

HRMS: (ESI) calculated for [$C_{16}H_{18}O$]: 227.1436 $[M+H]^+$, found 227.1427

Z:E ratio: >20:1; see spectral data section for NOESY analysis

1-(3-(Benzyloxy)penta-1,3-dien-2-yl)-4-methoxybenzene (9)

Notebook: DJL-5-036



Purification: column chromatography on silica gel eluting with 1 CV hexanes then 1% (ether : hexanes), clear colorless oil, (0.40 mmol scale) 90.4 mg, 81%.

TLC: R_f = 0.57, for *E/Z* mixture (10% ether : hexanes), UV, I_2, vanillin stain (maroon spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.50 – 7.29 (m, 7H), 7.00 – 6.87 (m, 2H), 5.44 – 5.36 (m, 1H), 5.29 – 5.24 (m, 1H), 4.67 (m, 1H), 3.85 – 3.82 (m, 3H), 1.69 – 1.62 (m, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 159.4, 154.9, 144.9, 138.1, 132.4, 129.4, 128.4, 128.2, 127.9, 113.7, 113.5, 112.6, 71.8, 55.4, 11.2

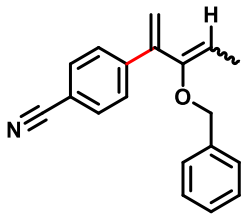
IR: 2932, 2844, 1716, 1607, 1513, 1248, 1170, 1030 cm^{-1}

Z:E ratio ~ (9:1), determined via ^{1}H NMR analysis of the methyl peaks ~ 1.6 ppm

Major peak *J* = 7.0 Hz, Minor peak *J* = 13.5 Hz

4-(3-(Benzyloxy)penta-1,3-dien-2-yl)benzonitrile (10)

Notebook: DJL-5-037



Purification: column chromatography on silica gel eluting with 10% then 25% (ether : hexanes), clear colorless oil, (0.40 mmol scale) 86.7 mg, 79%.

TLC: R_f = 0.26, for *E/Z* mixture (10% ether : DCM), UV, I_2, vanillin stain (spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.69 – 7.43 (m, 4H), 7.42 – 7.21 (m, 5H), 5.56 (s, 1H), 5.38 – 5.33 (1, H), 5.11 – 4.99 (m, 1H), 4.64 (s, 2H), 1.72 – 1.66 (d *J* = 6.50 Hz, 2H)

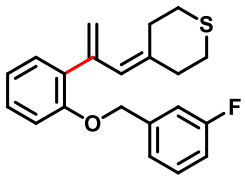
^{13}C NMR: (126 MHz, $CDCl_3$) δ 153.7, 144.6, 144.3, 137.5, 132.3, 132.1, 128.9, 128.5, 128.1, 128.1, 127.3, 119.0, 116.7, 114.3, 111.5, 72.1, 11.3

IR: 3072, 2984, 2937, 2875, 2235, 1721, 1456, 1279, 1019, 697 cm^{-1}

Z:E ratio ~ (9:1), *via* ^{1}H NMR analysis of the methyl peaks ~ 1.6 ppm, Major *J* = 6.5 Hz

4-(2-(2-((3-Fluorobenzyl)oxy)phenyl)allylidene)tetrahydro-2*H*-thiopyran (11)

Notebook: DJL-5-158



Purification: column chromatography on silica gel eluting with 1 CV hexanes then 2% then 5% (ether : hexanes), clear colorless oil, (0.40 mmol scale) 122.2 mg, 90%.

TLC: R_f = 0.39 (5% ether : hexanes), UV, I_2, vanillin stain (vibrant fuchsia spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.36 – 7.14 (m, 5H), 7.03 – 6.88 (m, 3H), 6.08 (s, 1H), 5.34 (d, *J* = 2.0 Hz, 1H), 5.25 (d, *J* = 1.5 Hz, 1H), 5.07 (s, 2H), 2.69 (m, 2H), 2.52 – 2.45 (m, 6H)

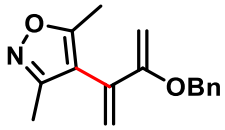
IR: 2906, 2828, 1721, 1487, 1440, 1232, 749 cm^{-1}

HRMS: (ESI) calculated for $[C_{21}H_{21}FOS]$: 341.1375 $[M+H]^+$, found 341.1364

***Note:** Rotamers of *s-cis* and *s-trans* diene moieties observed with bulky, yet flexible, *-ortho* aromatic groups.

4-(3-(Benzyloxy)buta-1,3-dien-2-yl)-3,5-dimethylisoxazole (12)

Notebook: DJL-7-263-B



Purification: column chromatography on silica gel eluting with 20% (ether : hexanes), clear colorless oil, (0.30 mmol scale) 74.1 mg, 97%.

TLC: R_f = 0.34 (20% ether : hexanes), UV, I_2, vanillin stain (tangerine spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 4H), 7.36 – 7.31 (m, 1H), 6.01 (d, *J* = 2.0 Hz, 1H), 5.12 (td, *J* = 1.8, 0.8 Hz, 1H), 4.89 (s, 2H), 4.32 (t, *J* = 2.1 Hz, 1H), 4.08 (d, *J* = 2.6 Hz, 1H), 2.31 (s, 3H), 2.17 (s, 3H)

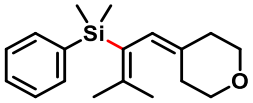
^{13}C NMR: (126 MHz, $CDCl_3$) δ 166.3, 159.6, 158.1, 137.0, 133.5, 128.6, 128.0, 127.4, 118.4, 115.1, 87.7, 69.9, 11.4, 10.5

IR: 3031, 2932, 1581, 1331, 1258, 1097, 697 cm^{-1}

HRMS: (ESI) calculated for $[C_{16}H_{17}NO_2]$: 256.1338 $[M+H]^+$, found 256.1344

Dimethyl(3-methyl-1-(tetrahydro-4*H*-pyran-4-ylidene)but-2-en-2-yl)(phenyl)silane (13)

Notebook: DJL-6-257-A



Purification: column chromatography on silica gel eluting with 1 CV hexanes then 5% (ether : hexanes), clear colorless oil, (0.30 mmol scale) 64.1 mg, 75%.

TLC: R_f = 0.24 (5% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 2H), 7.33 (m, 3H), 5.70 (dd, *J* = 3.0, 1.5 Hz, 1H), 3.69 – 3.66 (m, 2H), 3.58 (t, *J* = 5.5 Hz, 2H), 2.27 – 2.23 (m, 2H), 2.07 (m, 2H), 1.71 (dd, *J* = 15.3, 1.6 Hz, 6H), 0.37 (s, 6H)

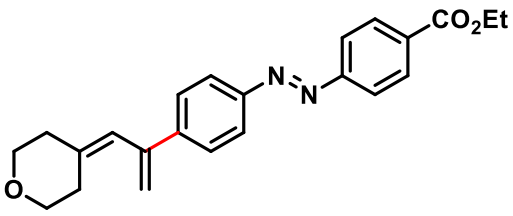
^{13}C NMR: (126 MHz, $CDCl_3$) δ 146.0, 140.3, 133.8, 133.4, 129.8, 128.7, 127.8, 126.2, 69.9, 68.5, 36.5, 30.8, 24.9, 23.3, -0.4

IR: 2958, 2838, 1607, 1430, 1232, 1102, 816 cm^{-1}

HRMS: (ESI) calculated for [$C_{18}H_{26}OSi$]: 287.1831 $[M+H]^+$, found 287.1844

Ethyl (*E*)-4-((4-(3-(tetrahydro-4*H*-pyran-4-ylidene)prop-1-en-2-yl)phenyl)diazenyl) benzoate (14)

Notebook: DJL-7-049



Purification: column chromatography on silica gel eluting with 20% then 40% (ether : hexanes), light orange solid, (0.30 mmol scale) 107.1 mg, 94%.

TLC: R_f = 0.19 (20% ether : hexanes), UV, material self stains on TLC plate

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.22 – 8.18 (m, 2H), 7.96 – 7.90 (m, 4H), 7.60 – 7.56 (m, 2H), 6.06 (d, *J* = 1.8 Hz, 1H), 5.65 (d, *J* = 1.6 Hz, 1H), 5.20 (d, *J* = 1.5 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.82 – 3.78 (m, 2H), 3.64 (t, *J* = 5.5 Hz, 2H), 2.41 (m, 2H), 2.35 – 2.32 (m, 2H), 1.43 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 155.3, 152.1, 144.4, 143.7, 140.1, 132.3, 130.7, 127.5, 123.4, 123.3, 122.7, 116.6, 69.7, 68.9, 61.4, 37.4, 31.4, 14.5

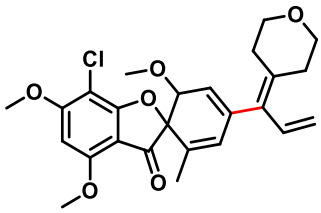
IR: 2983, 2953, 2838, 1710, 1269, 1097 cm^{-1}

HRMS: (ESI) calculated for [$C_{23}H_{24}N_2O_3$]: 399.1685 $[M+Na]^+$, found 399.1702

*Predominately *trans*-azo-isomer

7-Chloro-4,6,6'-trimethoxy-2'-methyl-4'-(1-(tetrahydro-4*H*-pyran-4-ylidene)allyl)-3*H*-spiro[benzofuran-2,1'-cyclohexane]-2',4'-dien-3-one (15)

Notebook: DJL-6-230



Purification: column chromatography on silica gel eluting with 40% then 60% (EtOAc : hexanes), clear yellow crystal, (0.20 mmol scale) 67.4 mg, 74%.

TLC: R_f = 0.19 (40% EtOAc : hexanes), UV, I_2, vanillin stain (light purple spot)

^{1}H NMR: (600 MHz, $CDCl_3$) δ 14.31 (s, 1H), 6.97 (dd, *J* = 17.0, 10.6 Hz, 1H), 6.49 (d, *J* = 42.1 Hz, 2H), 5.93 (s, 1H), 5.13 (dd, *J* = 10.7, 1.9 Hz, 1H), 4.73 (dd, *J* = 17.0, 2.0 Hz, 1H),

3.96 (s, 3H), 3.80 (t, *J* = 5.5 Hz, 2H), 3.68 (s, 3H), 3.63 (t, *J* = 5.4 Hz, 2H), 3.44 (s, 3H), 2.61 (t, *J* = 5.5 Hz, 2H), 2.14 (m, *J* = 14.8 Hz, 5H)

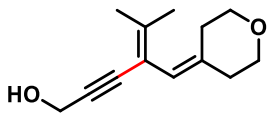
^{13}C NMR: (150 MHz, $CDCl_3$) δ 200.5, 162.2, 162.0, 161.9, 155.5, 140.4, 135.6, 134.5, 134.3, 134.2, 131.3, 124.0, 116.6, 109.8, 107.7, 69.2, 68.9, 56.4, 56.0, 55.8, 33.7, 30.8, 25.0, 19.0

IR: 2958, 2854, 1601, 1575, 1414, 1217, 1128, 1097 cm^{-1}

HRMS: (ESI) calculated for [$C_{25}H_{27}ClO_6$]: 481.1394 $[M+Na]^+$, found 481.1400

5-Methyl-4-((tetrahydro-4*H*-pyran-4-ylidene)methyl)hex-4-en-2-yn-1-ol (16)

Notebook: DJL-6-251-A



Purification: column chromatography on silica gel eluting with 60% (ether : hexanes), clear colorless oil, (0.30 mmol scale) 56.7 mg, 92%.

TLC: R_f = 0.12 (40% ether : hexanes), UV, I_2, vanillin stain (deep purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.81 – 5.63 (m, 1H), 4.41 (d, *J* = 2.8 Hz, 2H), 3.73 – 3.69 (m, 2H), 3.66 (t, *J* = 5.5 Hz, 2H), 2.41 – 2.37 (m, 2H), 2.28 – 2.25 (m, 2H), 1.98 (m, 4H), 1.74 (s, 3H)

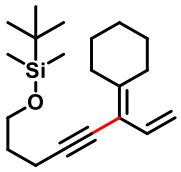
^{13}C NMR: (126 MHz, $CDCl_3$) δ 144.2, 138.0, 120.1, 113.5, 89.9, 85.6, 69.5, 68.5, 51.8, 36.9, 31.2, 23.3, 21.0

IR: 3392, 2911, 2854, 2209, 1367, 1092, 1019, 998 cm^{-1}

HRMS: (ESI) calculated for [$C_{13}H_{18}O_2$]: 206.1307 $[M+H]^+$, found 206.1305

***tert*-Butyl((6-cyclohexylideneoct-7-en-4-yn-1-yl)oxy)dimethylsilane (17)**

Notebook: DJL-4-120



Purification: column chromatography on silica gel eluting with 100% pentanes, clear colorless oil, (0.30 mmol scale) 83.8 mg, 88%.

TLC: R_f = 0.66 (10% ether : hexanes), UV, I_2

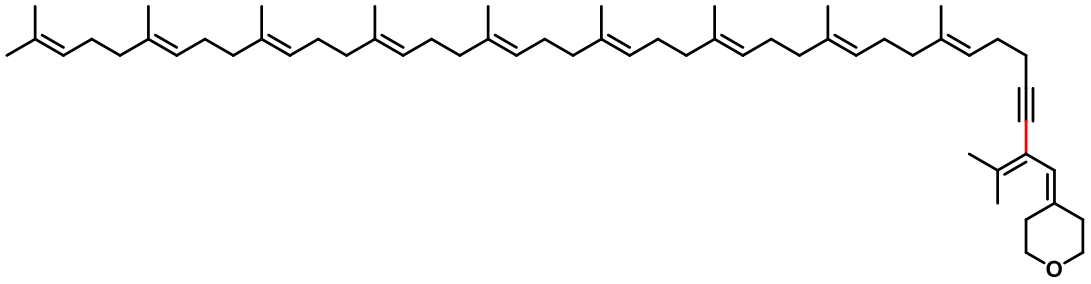
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.75 (dd, *J* = 16.7, 10.3 Hz, 1H), 5.60 (dd, *J* = 16.8, 2.1 Hz, 1H), 5.14 (dd, *J* = 10.4, 2.1 Hz, 1H), 3.74 (t, *J* = 6.2 Hz, 2H), 2.56 (t, *J* = 5.8 Hz, 2H), 2.49 (t, *J* = 7.0 Hz, 2H), 2.38 (t, *J* = 5.7 Hz, 2H), 1.83 – 1.76 (m, 2H), 1.64 – 1.54 (m, 6H), 0.90 (s, 9H), 0.06 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 149.9, 131.8, 115.4, 115.2, 94.5, 77.0, 62.0, 34.7, 32.3, 30.2, 28.1, 28.0, 26.8, 26.1, 18.5, 16.1, -5.2

IR: 2937, 2854, 2230, 1253, 832 cm^{-1}

4-((7*E*,11*E*,15*E*,19*E*,23*E*,27*E*,31*E*,35*E*)-8,12,16,20,24,28,32,36,40-Nonamethyl-2-(propan-2-ylidene)hentetraconta-7,11,15,19,23,27,31,35,39-nonaen-3-yn-1-ylidene)tetrahydro-2*H*-pyran (18)

Notebook: DJL-6-257-C



Purification: column chromatography on silica gel eluting with 1 CV hexanes then 5% (ether : hexanes), clear/ light bronze oil, (0.30 mmol scale) 216.7 mg, 90%.

TLC: R_f = 0.26 (5% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.76 (s, 1H), 5.20 (m, 1H), 5.14 – 5.09 (m, 8H), 3.72 (t, *J* = 5.5 Hz, 2H), 3.67 (t, *J* = 5.5 Hz, 2H), 2.50 – 2.44 (m, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.29 – 2.22 (m, 4H), 2.07 (m, 18H), 2.00 – 1.97 (m, 17H), 1.74 (s, 3H), 1.68 (s, 3H), 1.60 (m, 27H)

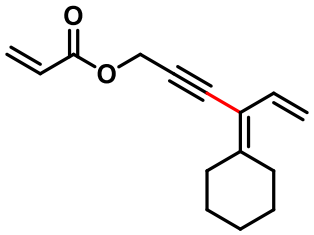
^{13}C NMR: (126 MHz, $CDCl_3$) δ 141.9, 137.4, 136.5, 135.2, 135.1, 135.1, 135.1, 135.1, 135.0, 135.0, 131.4, 124.6, 124.4, 124.4, 124.4, 124.4, 124.3, 123.1, 120.7, 114.4, 92.7, 80.5, 69.7, 68.7, 39.9, 39.9, 39.9, 37.1, 31.2, 27.9, 26.9, 26.9, 26.9, 26.8, 26.8, 25.8, 23.2, 20.9, 20.2, 17.8, 16.3, 16.2, 16.2, 16.2

IR: 2958, 2916, 2844, 1664, 1440, 1383, 1102, 848 cm^{-1}

HRMS: (ESI) calculated for $[C_{58}H_{90}O]$: 825.6890 $[M+Na]^+$, found 825.6909

4-Cyclohexylidenehex-5-en-2-yn-1-yl acrylate (21)

Notebook: DJL-5-214



Purification: column chromatography on silica gel eluting with 1 CV hexanes then 5% (ether : hexanes), clear/ light bronze oil, (0.50 mmol scale) 83.0 mg, 72%.

TLC: R_f = 0.45 (10% ether : hexanes), UV, I_2, vanillin stain (deep purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 16.8, 10.4 Hz, 1H), 6.46 (dd, *J* = 17.3, 1.4 Hz, 1H), 6.16 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.87 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.60 (dd, *J* = 16.9, 1.9 Hz, 1H), 5.17 (dd, *J* = 10.4, 1.9 Hz, 1H), 4.99 (s, 2H), 2.55 (t, *J* = 5.9 Hz, 2H), 2.39 (m, 2H), 1.66 – 1.57 (m, 6H)

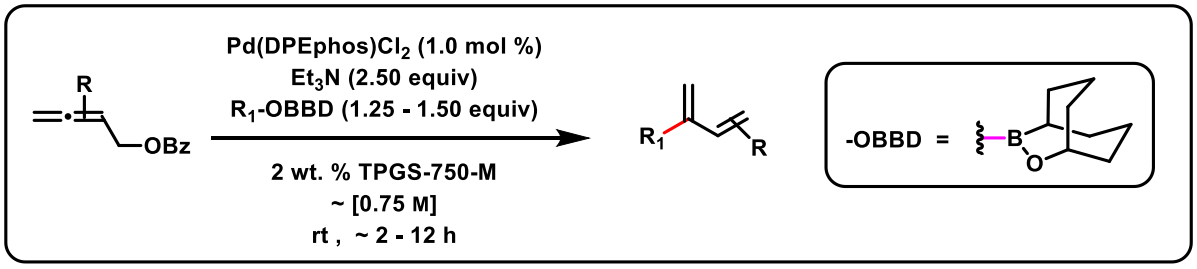
^{13}C NMR: (126 MHz, $CDCl_3$) δ 165.6, 152.8, 131.6, 131.0, 128.1, 115.9, 114.2, 87.6, 83.5, 53.3, 34.8, 30.3, 28.1, 28.0, 26.7

IR: 2927, 2854, 2225, 1731, 1404, 1165 cm^{-1}

HRMS: (ESI) calculated for $[C_{15}H_{18}O_2]$: 231.1385 $[M+H]^+$, found 231.1375

3.2 General procedure 'B'

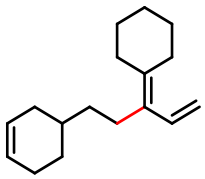
OBBD derivative-mediated sp^2-sp^3 cross-couplings



***Reactions utilizing –OBBD derivatives were performed analogously as described for general procedure **'A.'**

4-(3-Cyclohexylidenepent-4-en-1-yl)cyclohex-1-ene (22)

Notebook: RTHL-7-005-C



Purification: column chromatography on silica gel eluting with 100%, clear colorless oil, (0.30 mmol scale) 37.4 mg, 54% (volatile compound).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.82 (dd, *J* = 17.5, *J* = 11 Hz, 1H), 5.67 (m, 2H), 5.17 (dd, *J* = 17, *J* = 1.5 Hz, 1H), 4.99 (dd, *J* = 11 Hz, *J* = 1 Hz, 1H), 2.37-2.21 (m, 6H), 2.19-2.11 (m, 1H), 2.09-2.01 (m, 2H), 1.84-1.65 (m, 2H), 1.62-1.50 (m, 7H), 1.35-1.19 (m, 3H)

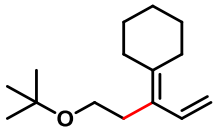
^{13}C NMR: (126 MHz, $CDCl_3$) δ 140.2, 134.3, 128.9, 127.2, 126.8, 111.3, 36.7, 34.3, 32.1, 31.7, 30.3, 29.1, 28.7, 28.5, 27.1, 25.5, 25.1

IR: 3082, 3025, 2920, 2851, 1624, 1446, 1352, 1263, 1232, 984, 908, 890, 733, 652 cm^{-1}

HRMS: (EI) calculated for [$C_{17}H_{26}$]: 230.2035 [M]$^{+\bullet}$, found 230.2035

(5-(*tert*-Butoxy)pent-1-en-3-ylidene)cyclohexane (23)

Notebook: RTHL-7-005-B



Purification: column chromatography on silica gel eluting with 100%, clear colorless oil, (0.30 mmol scale) 42.7 mg, 64% (volatile compound).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.83 (dd, *J* = 17, *J* = 11 Hz, 1H), 5.23 (d, *J* = 17.5 Hz, 1H) 5.00 (d, *J* = 11.5 Hz, 1H), 3.30 (t, *J* = 8 Hz, 2H), 2.54 (t, *J* = 8 Hz, 2H), 2.36- 2.21 (m, 4H), 1.65-1.48 (m, 6H), 1.18 (s, 9H)

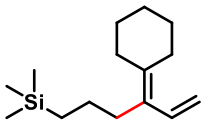
^{13}C NMR: (126 MHz, $CDCl_3$) δ 142.3, 134.4, 124.9, 111.6, 72.8, 61.1, 31.9, 30.4, 29.3, 28.8, 28.5, 27.7, 27.1

IR: 3093, 2973, 2925, 1726, 1627, 1445, 1361, 1272, 1195, 1072, 907, 892, 733, 711 cm^{-1}

HRMS: (EI) calculated for [$C_{15}H_{26}O$]: 222.1984 [M]$^{+\bullet}$, found 222.1988

(4-Cyclohexylidenehex-5-en-1-yl)trimethylsilane (24)

Notebook: RTHL-7-005-A



Purification: column chromatography on silica gel eluting with 100% hexanes, clear colorless oil, (0.30 mmol scale) 46.1 mg, 65% (volatile compound).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.82 (dd, *J* = 17.5, *J* = 11 Hz, 1H), 5.16 (dd, *J* = 17.5 Hz, *J* = 1.5 Hz, 1H), 5.00 (dd, *J* = 11.5 Hz, *J* = 1.5 Hz, 1H), 2.34 (t, *J* = 6 Hz, 2H), 2.28-2.21 (m, 4H), 1.61-1.52 (m, 6H), 1.40-1.31 (m, 2H), 0.57-0.50 (m, 2H), -0.03 (s, 9H)

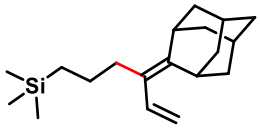
^{13}C NMR: (126 MHz, $CDCl_3$) δ 140.4, 134.5, 128.9, 111.4, 31.8, 31.7, 30.3, 28.7, 28.5, 27.2, 24.2, 17.5, -1.5

IR: 2925, 2854, 1625, 1247, 860, 833, 734 cm^{-1}

HRMS: (EI) calculated for [$C_{15}H_{28}Si$]: 236.1960 $[M]^{+\bullet}$, found 236.1957

(4-((1*r*,3*r*,5*R*,7*S*)-Adamantan-2-ylidene)hex-5-en-1-yl)trimethylsilane (25)

Notebook: RTHL-7-010



Purification: column chromatography on silica gel eluting with 100% hexanes, clear colorless oil, (0.30 mmol scale) 75.3 mg, 87%.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.81 (dd, *J* = 17.5, *J* = 11 Hz, 1H), 5.17 (dd, *J* = 17 Hz, *J* = 1.5 Hz, 1H), 4.97 (dd, *J* = 11 Hz, *J* = 1.5 Hz, 1H), 3.16 (s, 1H), 2.91 (s, 1H), 2.26 (m, 2H), 1.99-1.80 (m, 8H), 1.79-1.67 (m, 4H), 1.40-1.31 (m, 2H), 0.58-0.50 (m, 2H), -0.02 (s, 9H)

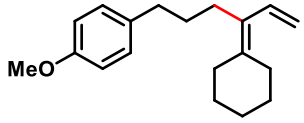
^{13}C NMR: (126 MHz, $CDCl_3$) δ 147.9, 134.1, 125.7, 111.1, 39.5, 39.4, 37.3, 34.1, 32.7, 31.4, 28.3, 24.3, 17.5, -1.5

IR: 3083, 2951, 2907, 1627, 1476, 1246, 1107, 988, 888, 850, 832, 755, 739, 690 cm^{-1}

HRMS: (EI) calculated for [$C_{19}H_{32}Si$]: 288.2273 $[M]^{+\bullet}$, found 288.2271

1-(4-Cyclohexylidenehex-5-en-1-yl)-4-methoxybenzene (26)

Notebook: RTHL-7-013-B



Purification: column chromatography on silica gel eluting with 0-2% (ether : hexanes), clear colorless oil, (0.30 mmol scale) 76.2 mg, 94%.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 11.4 Hz, 2H), 6.82 (dd, *J* = 17.4 Hz, *J* = 10.8 Hz, 1H), 5.08 (d, *J* = 16.2 Hz, 1H) 4.97 (d, *J* = 10.8 Hz, 1H), 3.80 (s, 3H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.34 (t, *J* = 6 Hz, 2H), 2.30 (m, 2H), 2.22 (t, *J* = 6 Hz, 2H), 1.69-1.65 (m, 2H), 1.64-1.50 (m, 6H)

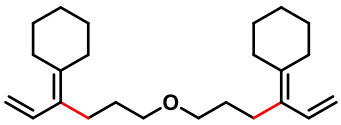
^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.8, 140.5, 134.8, 134.3, 129.4, 128.5, 113.8, 111.4, 55.4, 35.4, 31.7, 31.5, 30.3, 28.7, 28.5, 27.2, 27.1

IR: 3088, 2923, 2859, 1721, 1612, 1511, 1451, 1270, 1243, 1175, 1038, 891, 826, 806, 712 cm^{-1}

HRMS: (EI) calculated for [$C_{19}H_{26}O$]: 270.1984 $[M]^{+\bullet}$, found 270.1982

(Oxybis(hex-1-en-6-yl-3-ylidene))dicyclohexane (27)

Notebook: RTHL-7-013-A



Purification: column chromatography on silica gel eluting with 100% hexanes, clear colorless oil, (0.30 mmol scale) 44.2 mg, 43%.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.82 (dd, *J* = 17.5 Hz, *J* = 11 Hz, 2H), 5.20 (dd, *J* = 17 Hz, *J* = 1 Hz, 2H), 4.99 (dd, *J* = 11 Hz, *J* = 1.5 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 4H), 2.37- 2.31 (m, 8H), 2.29 2.24 (m, 4H), 1.67-1.61 (m, 4H), 1.60-1.50 (m, 12H)

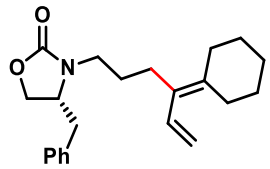
^{13}C NMR: (126 MHz, $CDCl_3$) δ 140.7, 134.2, 128.2, 111.6, 70.8, 31.7, 30.4, 29.8, 28.7, 28.5, 27.1, 24.0

IR: 3093, 2924, 2852, 2251, 1624, 1447, 1115, 985, 906, 852, 731, 649 cm^{-1}

HRMS: (EI) calculated for [$C_{24}H_{38}O$]: 342.2923 $[M]^{+\bullet}$, found 342.2911

(*R*)-4-Benzyl-3-(4-cyclohexylidenehex-5-en-1-yl)oxazolidin-2-one (28)

Notebook: RTHL-7-031-A



Purification: column chromatography on silica gel eluting with 0-10-20-25% (ethyl acetate : hexanes), clear colorless oil, (0.30 mmol scale) 95.1 mg, 93%.

Note: Product can co-eluted with the borabicyclodecanol formed during transmetallation.

TLC: R_f = 0.30 (20% EtOAc : hexanes), UV, I_2, vanillin stain

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.28-7.03 (m, 5H), 6.73 (dd, *J* = 17.4 Hz, *J* = 10.8 Hz, 1H), 5.05 (d, *J* = 17.4 Hz 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 4.30 (br, s, 1H), 4.11-4.02 (m, 1H), 3.98-3.88 (m, 2H), 3.50-3.42 (m, 1H), 3.06-2.96 (m, 2H), 2.63-2.53 (m, 1H), 2.31-2.10 (m, 6H), 1.85-1.69 (m, 4H), 1.66-1.29 (m, 16H)

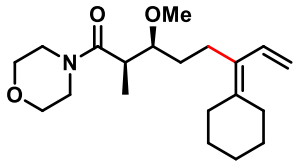
^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.1, 141.0, 135.7, 134.1,129.0, 129.0, 127.4, 127.3, 111.6, 71.0, 66.8, 56.0, 42.2, 38.6, 32.1, 31.7, 30.3, 29.0, 28.4, 27.1, 26.9, 26.3, 24.5, 22.1

IR: 3092, 3029, 2922, 2854, 1746, 1450, 1412, 1386, 1340, 1300, 1251, 732, 700 cm^{-1}

HRMS: (ESI) calculated for $[C_{22}H_{29}NO_2Na]^+$: 362.2091 $[M+Na]^+$, found 362.2094

(2*R*,3*S*)-6-Cyclohexylidene-3-methoxy-2-methyl-1-morpholinooct-7-en-1-one (29)

Notebook: RTHL-7-031-B



Purification: column chromatography on silica gel eluting with 50% (ethyl acetate : hexanes), clear colorless oil, (0.30 mmol scale) 78.1 mg, 77%.

TLC: R_f = 0.10 (20% EtOAc : hexanes), UV, I_2, vanillin stain

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 17.5 Hz, *J* = 11 Hz, 1H), 5.16 (dd, *J* = 17.5 Hz, *J* = 1 Hz, 1H), 4.98 (dd, *J* =11 Hz, *J* = 1 Hz, 1H), 3.70-3.50 (m, 8H), 3.44 (s, 3H), 3.41 (dt, *J* = 7Hz, *J* = 2Hz, 1H), 2.85 (p, *J* = 7Hz, 1H), 2.36-2.17 (m, 6H), 1.70-1.39 (m, 12H), 1.21 (d, *J* = 7 Hz, 3H)

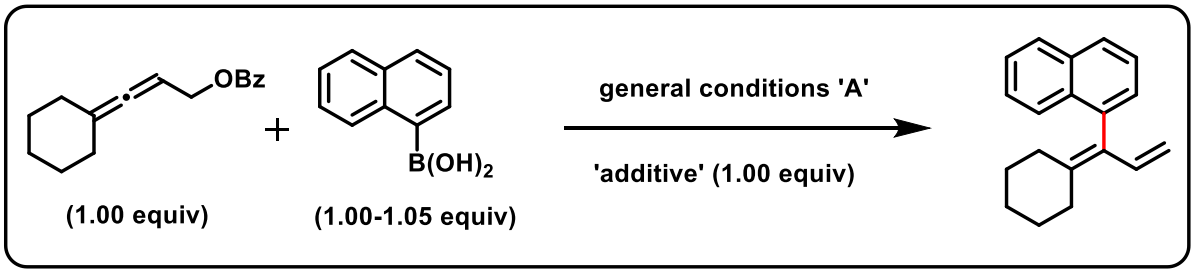
^{13}C NMR: (126 MHz, $CDCl_3$) δ 173.6, 140.6, 134.2, 128.3, 111.5, 83.8, 71.1, 67.1, 67.0, 58.6, 46.4, 42.2, 39.6, 31.6, 30.3, 28.7, 28.5, 27.1, 26.4, 22.2, 15.2

IR: 3092, 2966, 2923, 2853, 2254, 1638, 1430, 1227, 1115, 1098, 1069, 1032, 894, 731 cm^{-1}

HRMS: (ESI) calculated for $[C_{20}H_{33}NO_3Na]^+$: 358.2353 $[M+Na]^+$, found 358.2350

3.3 General procedure ‘C’

Robustness screen

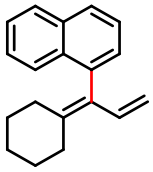


$Pd(DPEphos)Cl_2$ (1-2 mg) was added to a microwave vial fitted with a spin vane, septum, and argon needle, followed by 0.4 mL of a 2 wt % solution of TPGS-750-M, and the mixture was stirred vigorously until homogeneous. Et_3N (0.05 mL) was added *via* syringe and the mixture was left stirring while the other reagents were weighed out. Naphthylboronic acid (51.6-54.2 mg, 0.300-0.315 mmol, 1.00-1.05 equiv) was added as a solid, followed immediately by 0.30 mmol (1.00 equiv) of the appropriate additive and then, quickly, 0.30 mmol (1.00 equiv) of the allenoate. The reaction was left to stir for *ca*. 30 min (reaction followed by TLC), and once complete, the mixture was diluted with EtOAc and the entire contents of the reaction vessel were filtered through a short plug of silica gel. Volatiles were removed under reduced pressure to afford a crude mixture of product and additive, which was purified by flash chromatography on silica gel, eluting with 0-100% (EtOAc : hexanes), isolating both the desired product and additive. Yields obtained of product and recovered additive, after removal of trace volatiles on high-vacuum, were used as a measure of the functional group tolerance of the reaction with respect to functionality in the additive.

*** All additives were commercially available, and the recovered compounds displayed identical spectrographic properties (^1H NMR and ^{13}C NMR).

1-(1-Cyclohexylideneallyl)naphthalene (30)

Notebook: RTHL-6-271/273/295, RTHL-7-004



Purification: column chromatography on silica gel (extra 1-2 inches of SiO_2) eluting with 100% hexanes, clear colorless oil, (0.30 mmol scale) 83 - 94%.

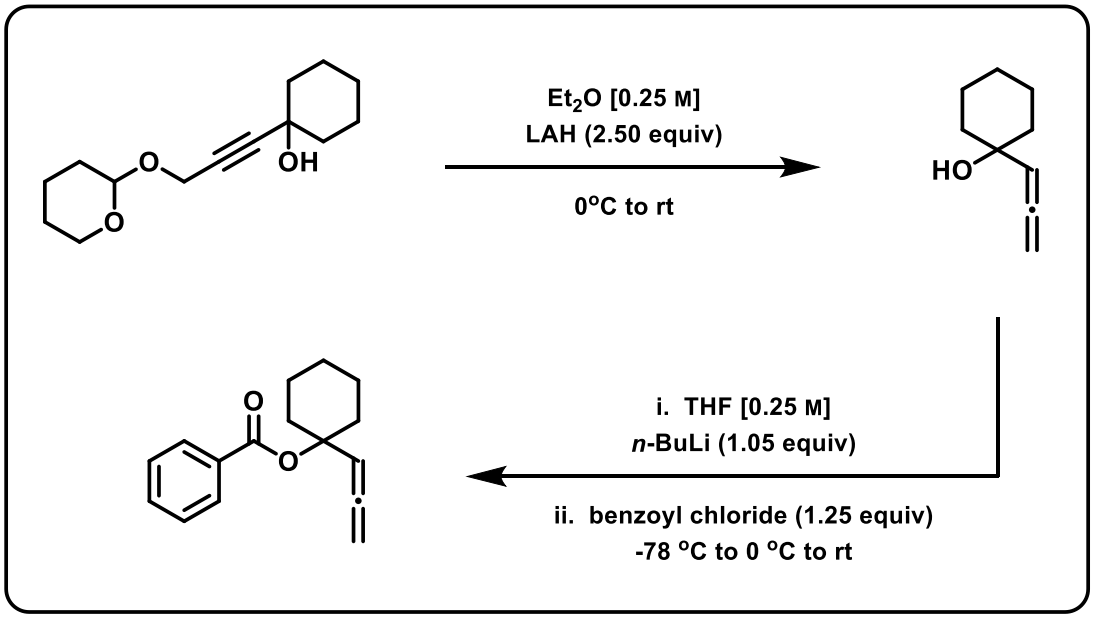
TLC: R_f = 0.60 (100% hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.90 – 7.85 (m, 1H), 7.84 – 7.77 (m, 2H), 7.53 – 7.39 (m, 3H), 7.20 (ddd, *J* = 17.1, 8.7, 4.2 Hz, 2H), 4.97 (dd, *J* = 10.7, 1.7 Hz, 1H), 4.36 (dd, *J* = 17.1, 1.7 Hz, 1H), 2.84 – 2.46 (m, 2H), 1.88 – 1.72 (m, 4H), 1.60 (tt, *J* = 14.2, 7.0 Hz, 2H), 1.45 – 1.35 (m, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 142.9, 138.3, 134.7, 133.8, 132.6, 130.5, 128.2, 127.4, 126.9, 126.2, 125.8, 125.7, 125.6, 115.6, 33.5, 30.3, 28.6, 28.4, 27.0

HRMS: (EI^+) calculated for [$C_{19}H_{20}$]: 248.1565 $[M]^{+\bullet}$, found 248.1563

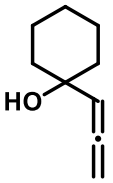
4. Scale-Up Example [2]



***Prepared according to known literature procedures.[2]

1-(Propa-1,2-dien-1-yl)cyclohexan-1-ol

Notebook: DJL-7-300



Purification: column chromatography on silica gel eluting with 20% then 30% (ether : hexanes), viscous clear colorless oil, (10.50 mmol scale) 978 mg, 67%.

TLC: R_f = 0.31 (30% ether : hexanes), UV, I_2, vanillin stain (grey/ lavender spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.29 (t, *J* = 6.7 Hz, 1H), 4.87 (dd, *J* = 6.8, 2.5 Hz, 2H), 1.68 – 1.59 (m, 7H), 1.47 (m, 3H), 1.34 (m, *J* = 5.2 Hz, 1H)

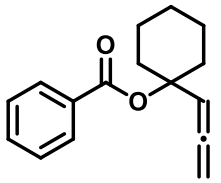
^{13}C NMR: (126 MHz, $CDCl_3$) δ 206.4, 99.5, 78.3, 70.6, 38.4, 25.6, 22.7

IR: 3356, 2930, 2855, 1957, 1450, 1053, 1036, 954, 843 cm^{-1}

HRMS: (ESI) calculated for $[C_9H_{14}O]$: 139.1123 $[M+H]^+$, found 139.1118

1-(Propa-1,2-dien-1-yl)cyclohexyl benzoate

Notebook: DJL-8-001



Purification: column chromatography on silica gel eluting with 1 CV hexanes, then 1% then 3% (ether : hexanes), viscous clear colorless oil, (6.23 mmol scale) 1.177 g, 78%.

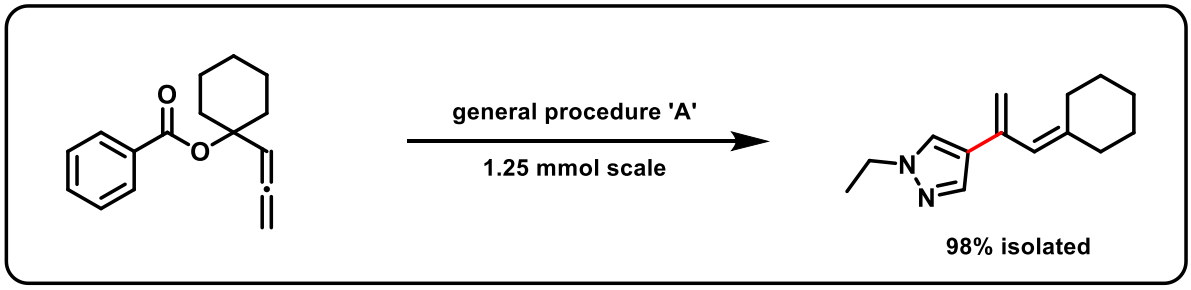
TLC: R_f = 0.47 (7% ether : hexanes), UV, I_2, vanillin stain (deep grey/ purple spot)

^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.56 – 7.52 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 5.78 (t, *J* = 6.7 Hz, 1H), 4.88 (d, *J* = 6.7 Hz, 2H), 2.33 (d, *J* = 12.2 Hz, 2H), 1.78 (m, 2H), 1.65 – 1.57 (m, 5H), 1.40 – 1.33 (m, 1H)

^{13}C NMR: (151 MHz, $CDCl_3$) δ 207.9, 165.4, 132.7, 131.8, 129.6, 128.4, 96.0, 81.4, 78.0, 35.6, 25.5, 22.4

IR: 2936, 2866, 1951, 1712, 1450, 1275, 1240, 1106, 1036, 715 cm^{-1}

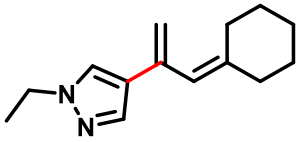
HRMS: (ESI) calculated for $[C_{16}H_{18}O_2]$: 265.1205 $[M+Na]^+$, found 265.1197



***Prepared according to general procedure **'A'** above.

4-(3-Cyclohexylideneprop-1-en-2-yl)-1-ethyl-1*H*-pyrazole

Notebook: DJL-8-002



Purification: column chromatography on silica gel eluting with 30% then 40% (ether : hexanes), faintly yellow clear oil, (1.25 mmol scale) 266 mg, 98%.

TLC: R_f = 0.17 (25% ether : hexanes), UV, I_2, vanillin stain (deep crimson spot)

^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.34 (s, 1H), 5.81 (d, *J* = 2.3 Hz, 1H), 5.35 (d, *J* = 2 Hz, 1H), 4.80 (t, *J* = 1.7 Hz, 1H), 4.11 (q, *J* = 7.3 Hz, 2H), 2.29 – 2.26 (m, 2H), 2.21 – 2.18 (m, 2H), 1.63 – 1.55 (m, 4H), 1.46 (t, *J* = 7.3 Hz, 5H)

^{13}C NMR: (151 MHz, $CDCl_3$) δ 144.4, 136.8, 136.1, 125.9, 123.7, 121.2, 110.2, 47.1, 37.5, 30.1, 28.9, 28.2, 26.8, 15.6

IR: 2989, 2925, 2855, 1613, 1444, 1053, 1036, 995, 849 cm^{-1}

HRMS: (ESI) calculated for $[C_{14}H_{20}N_2]$: 217.1705 $[M+H]^+$, found 217.1711

1.6. Experimental References

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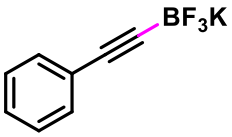
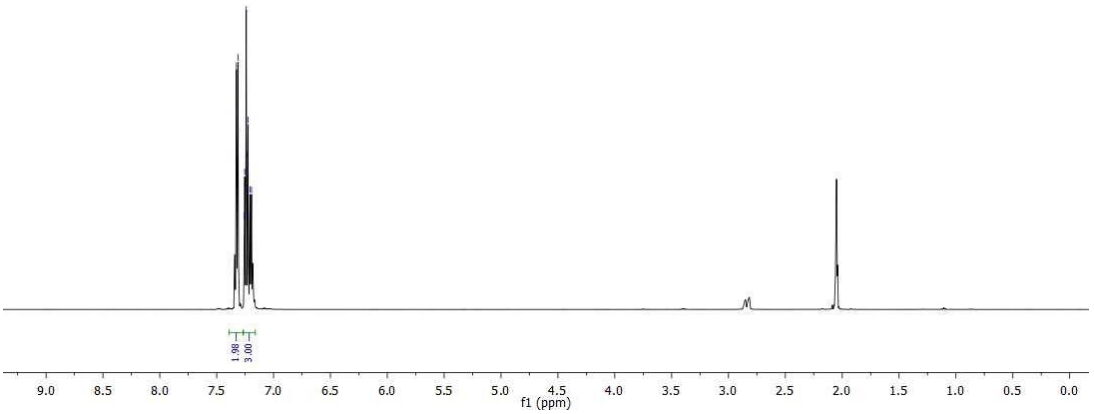
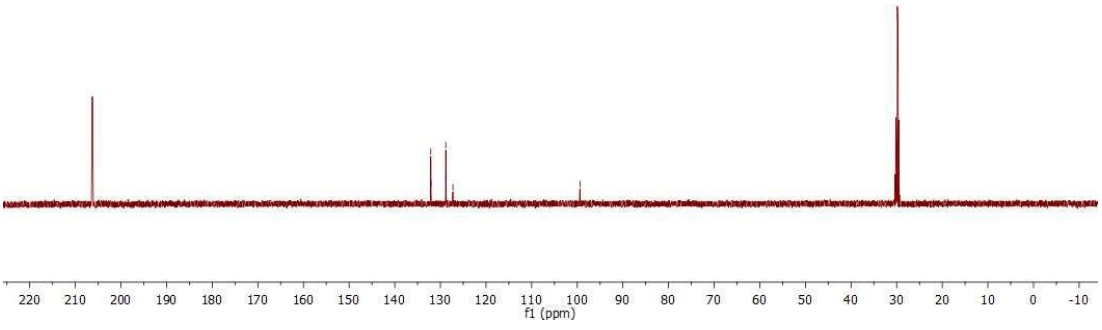
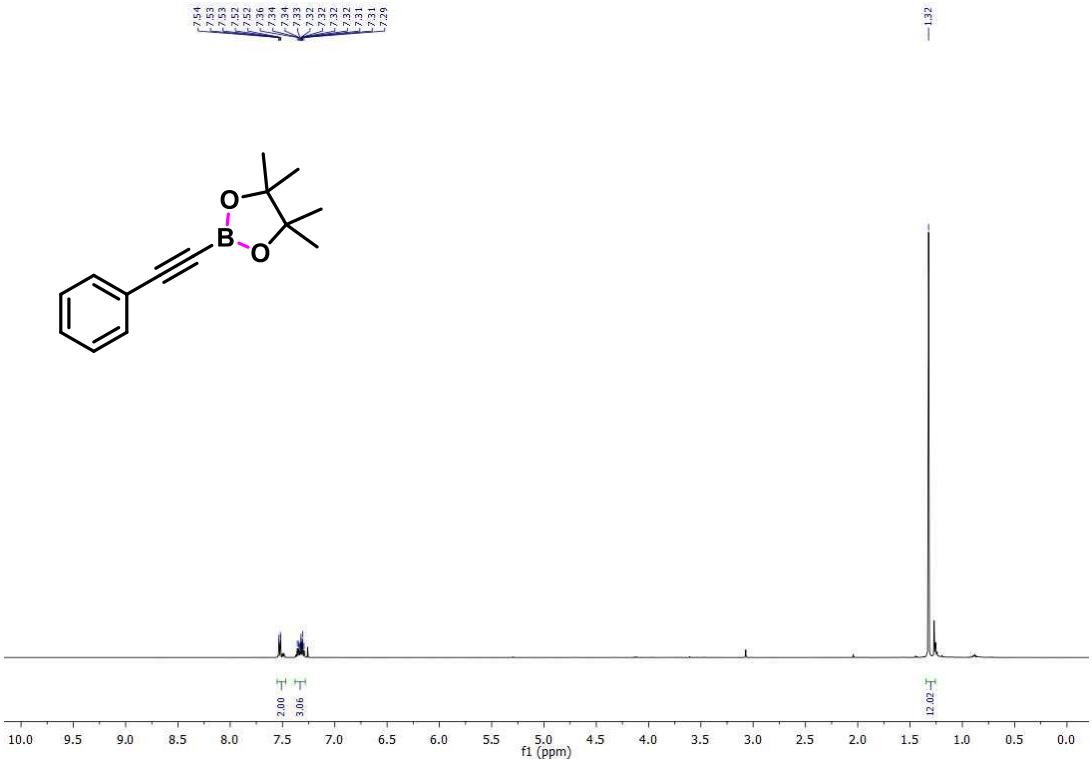
7. Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044.

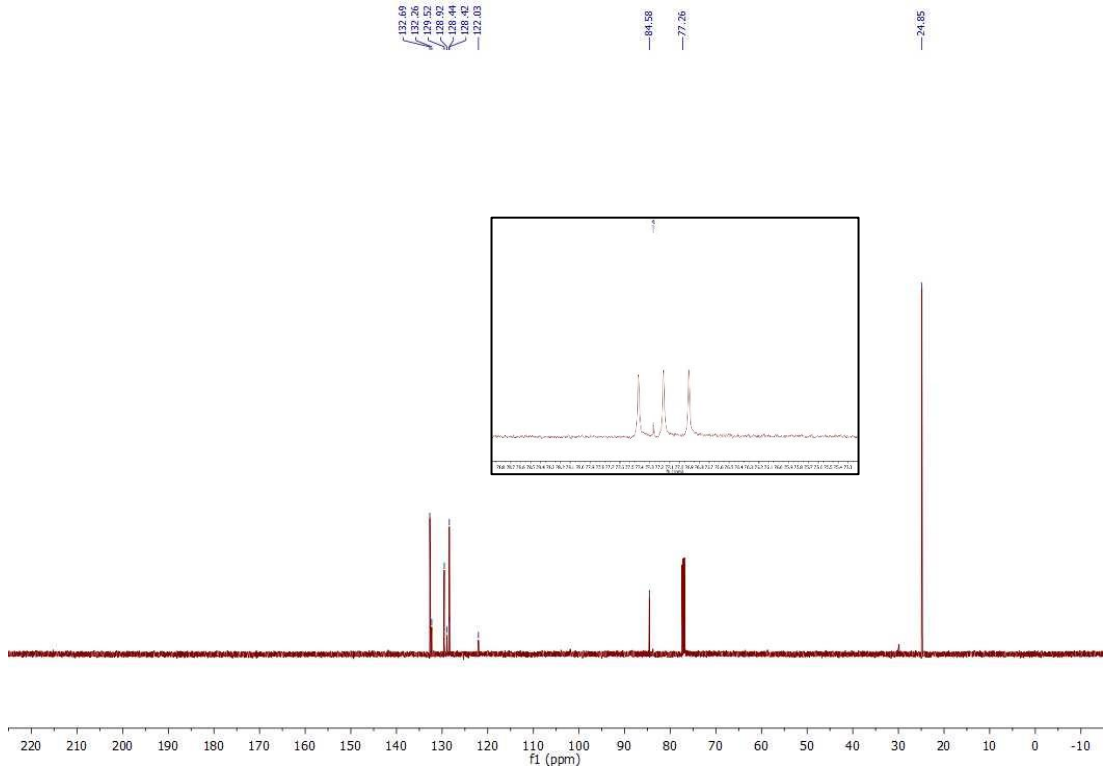
1.7. Spectral Data

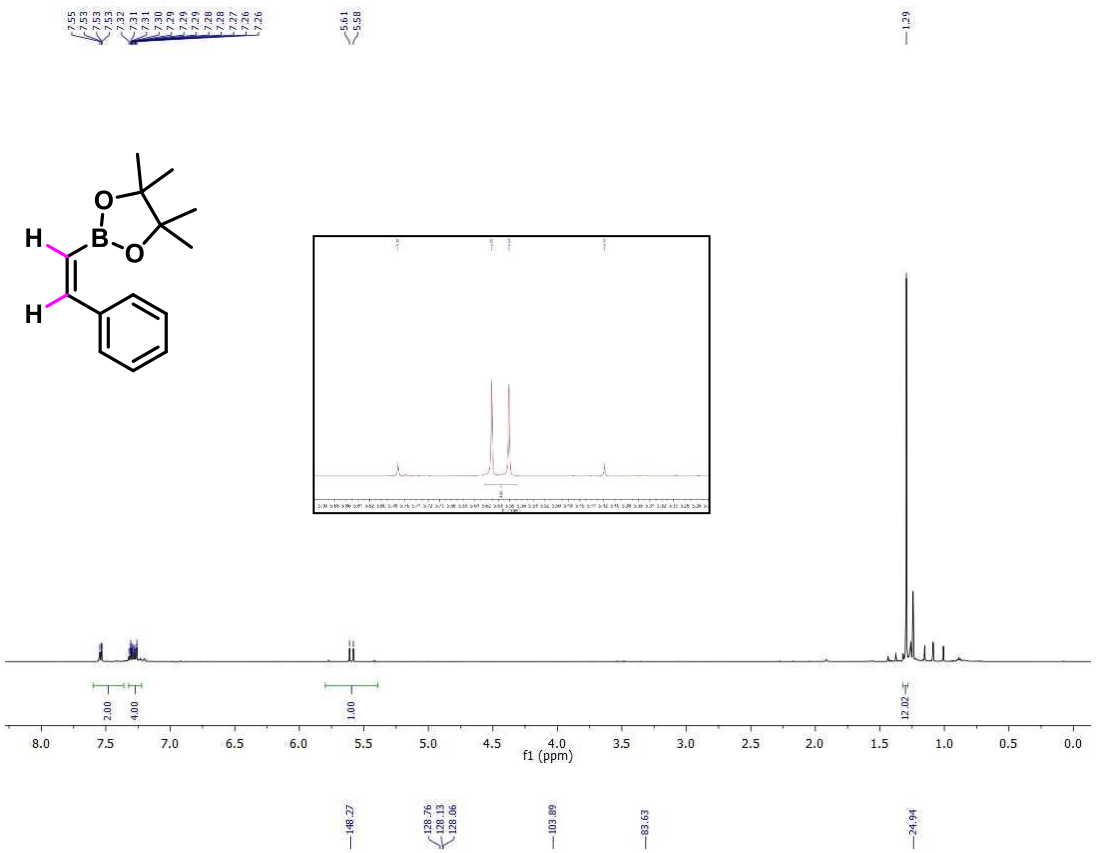


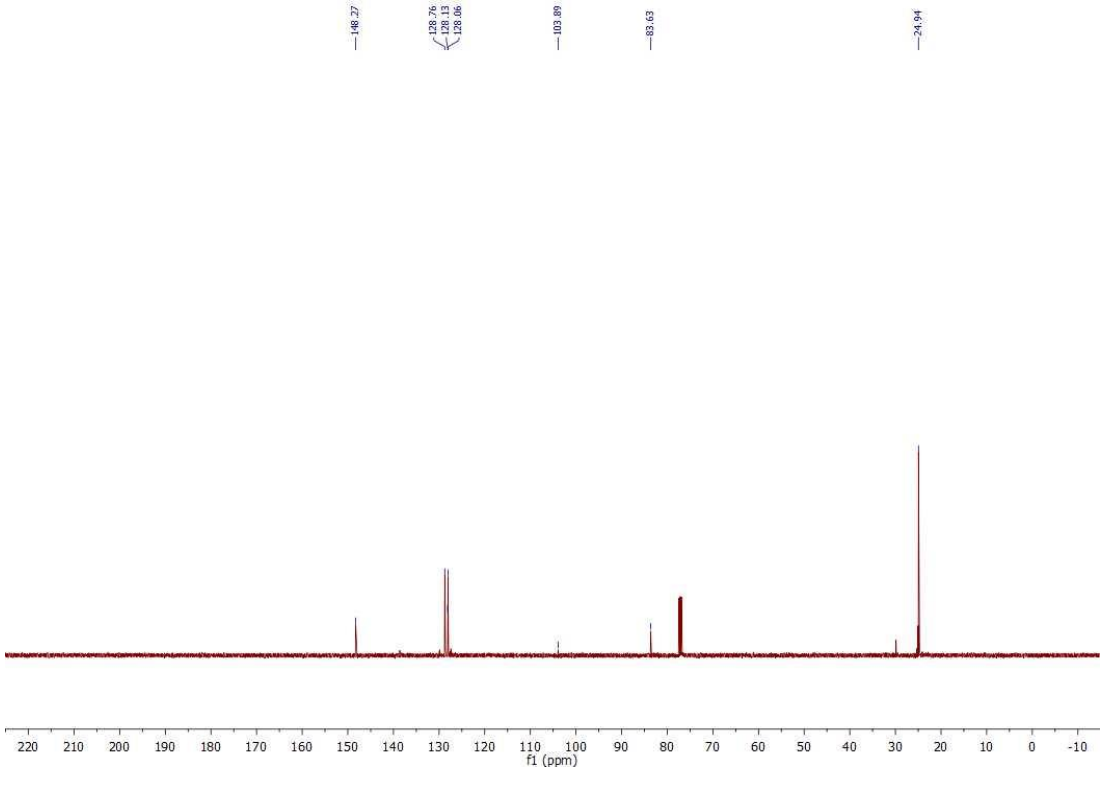


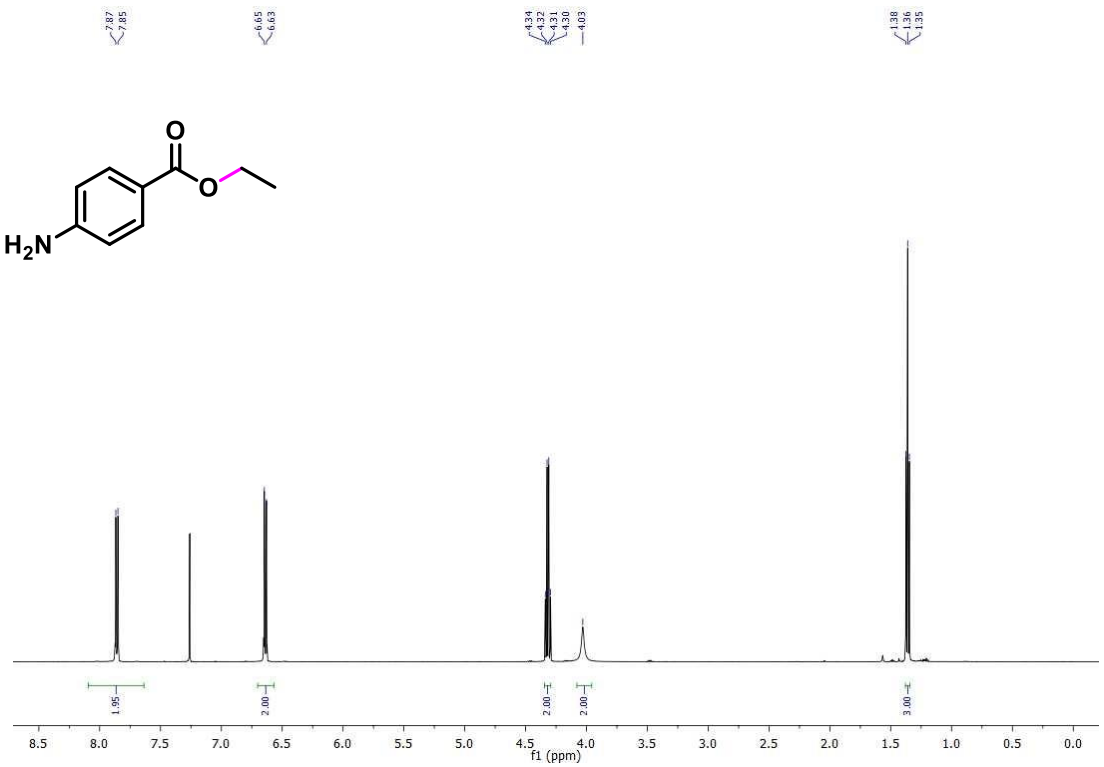


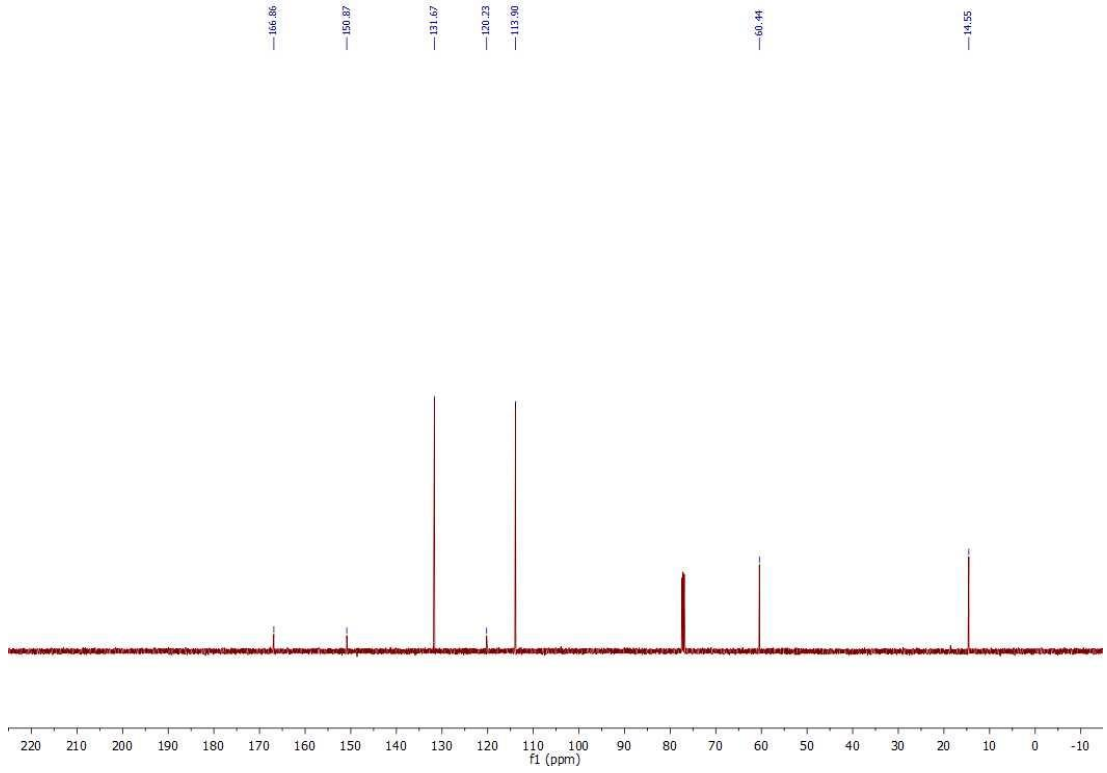

7.54
7.53
7.53
7.52
7.52
7.36
7.34
7.34
7.33
7.32
7.32
7.32
7.32
7.31
7.31
7.29
1.32
O
B
O
O
2.00
3.06
12.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

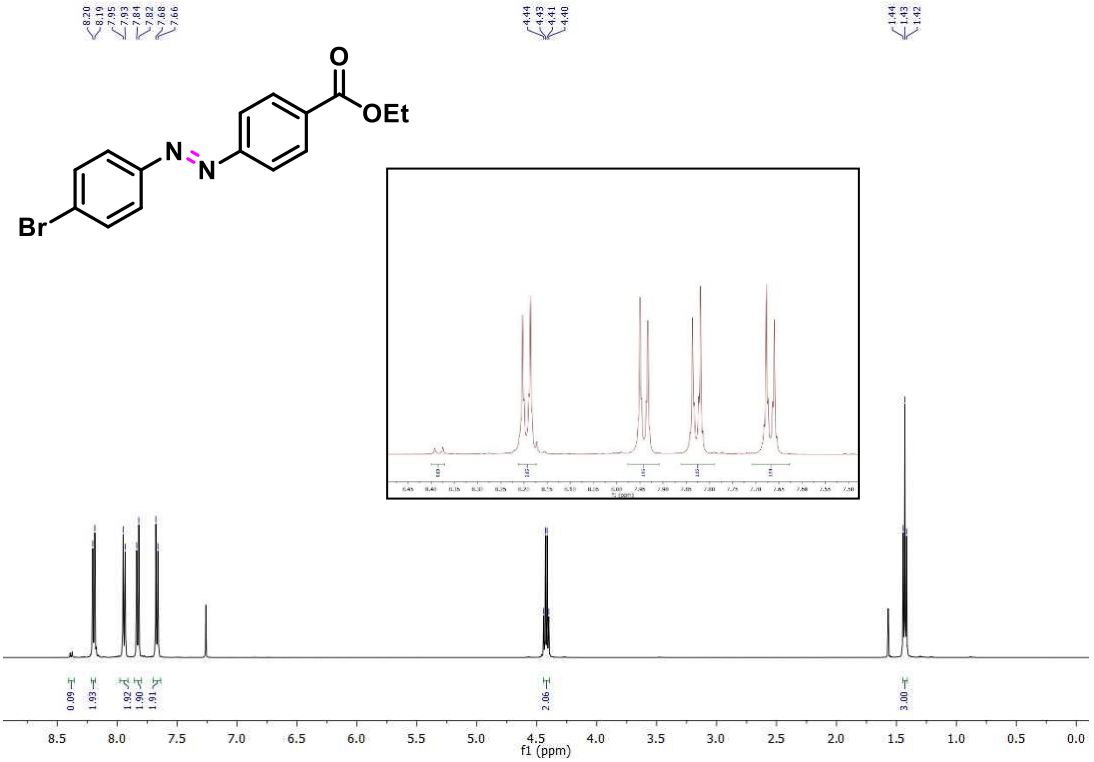

132.69
132.26
129.52
128.92
128.44
128.42
122.03
84.58
77.26
24.85
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

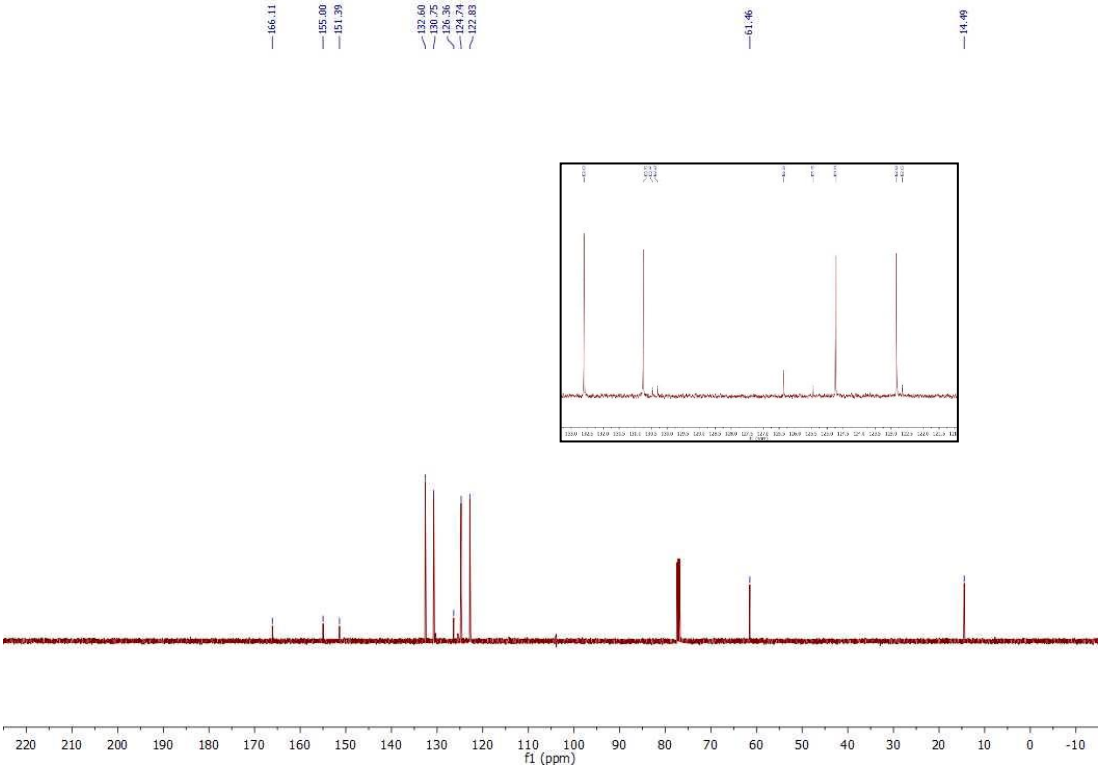

7.55
7.53
7.53
7.53
7.32
7.31
7.31
7.30
7.29
7.29
7.29
7.28
7.28
7.27
7.26
7.26
5.61
5.58
1.29
O
B
O
H
H
2.00
4.00
1.00
12.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

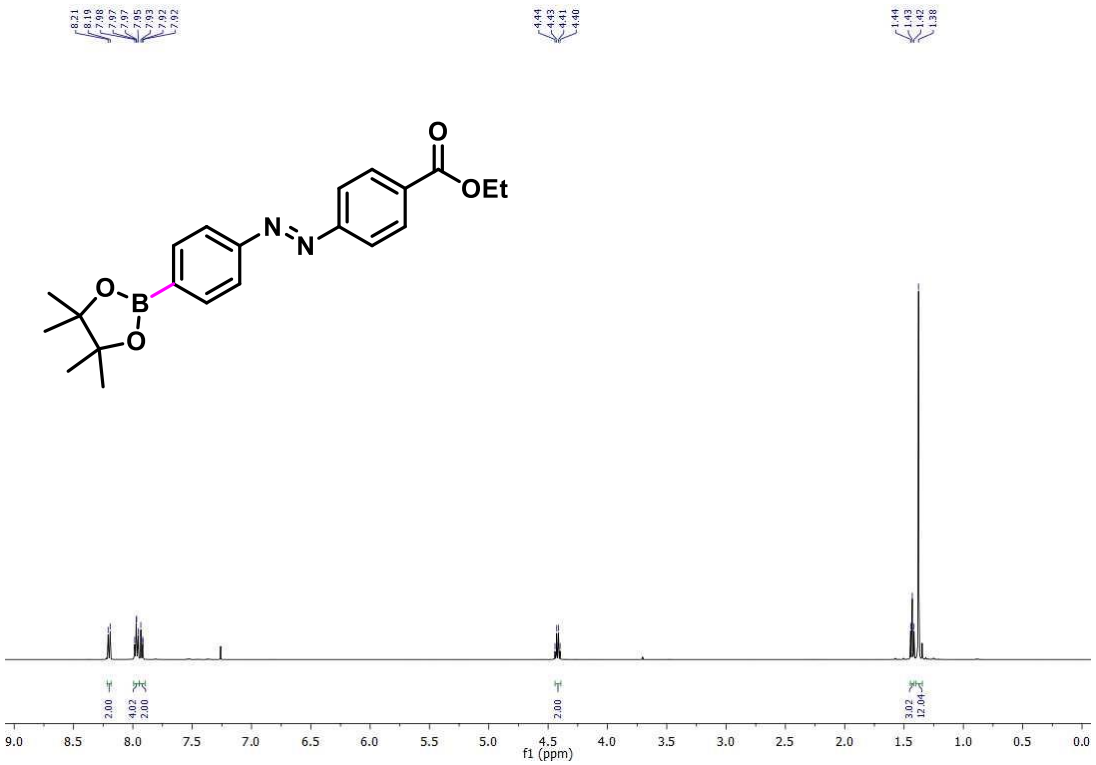

148.27
128.76
128.13
126.06
103.89
83.63
24.94
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

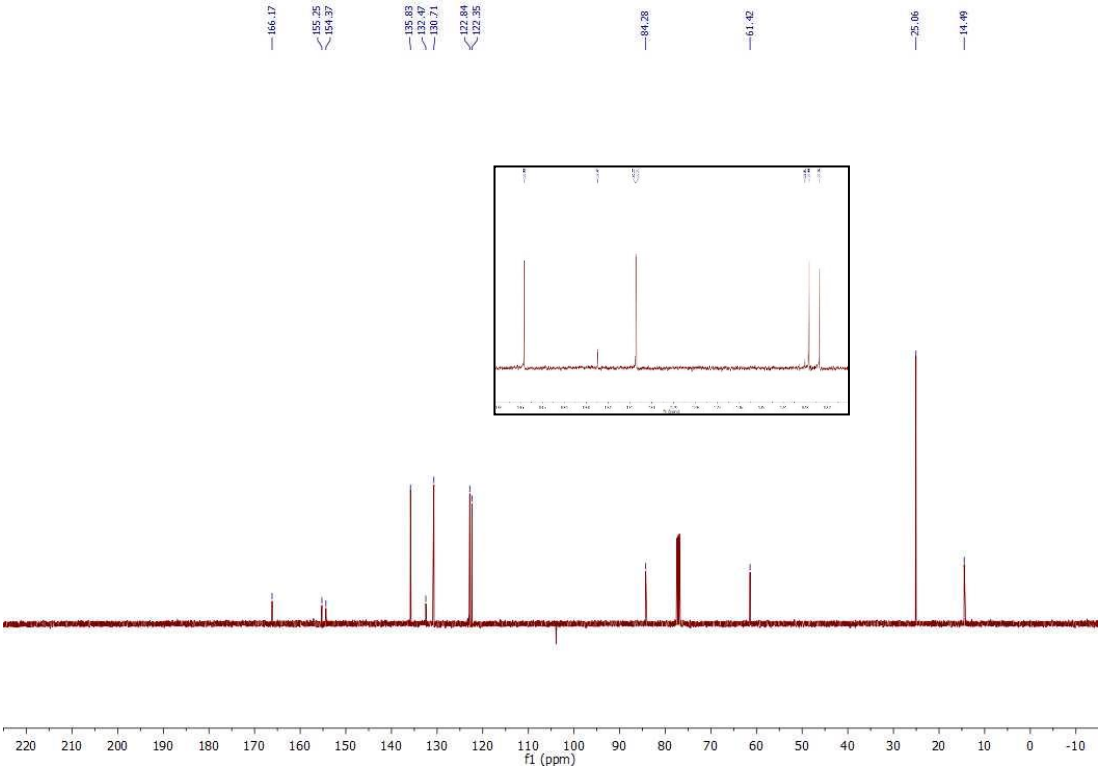

7.87
7.85
6.65
6.63
4.34
4.32
4.31
4.30
4.03
1.38
1.36
1.35
O
O
H2N
1.95
2.00
2.00
2.00
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

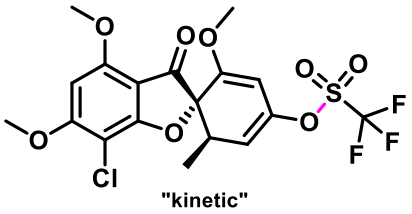

166.86
150.87
131.67
120.23
113.90
60.44
14.55
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


8.20
8.19
7.95
7.93
7.84
7.82
7.68
7.66
4.44
4.43
4.41
4.40
1.44
1.43
1.42
O
OEt
N
N
Br
0.09
1.93
1.92
1.90
1.91
2.06
3.00
f1 (ppm)

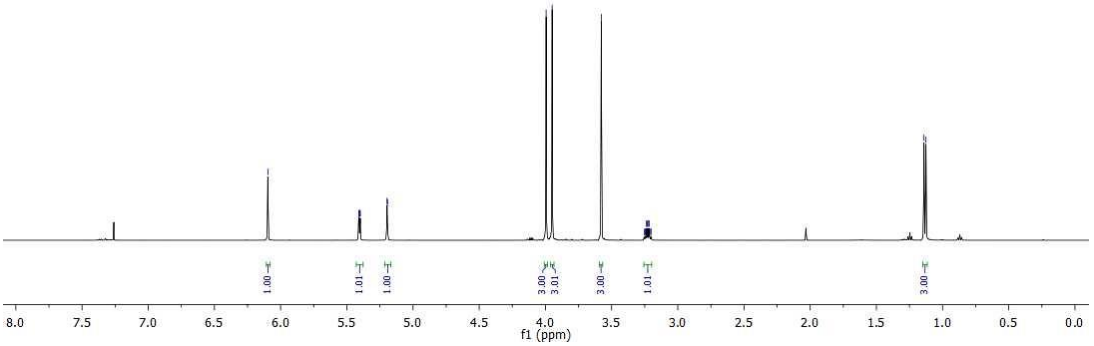

166.11
155.00
151.39
132.60
130.75
126.36
124.74
122.83
61.46
14.49
f1 (ppm)

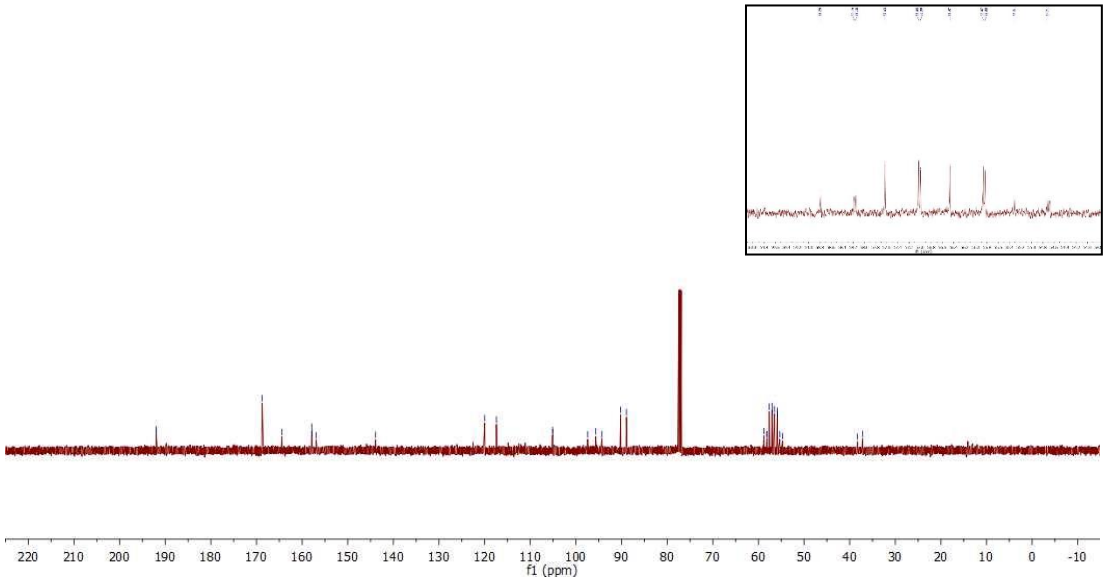

8.21
8.19
7.98
7.97
7.97
7.95
7.93
7.92
7.92
4.44
4.43
4.41
4.40
1.44
1.43
1.42
1.38
O
OEt
N
N
O
B
O
2.00
4.02
2.00
2.00
3.02
12.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

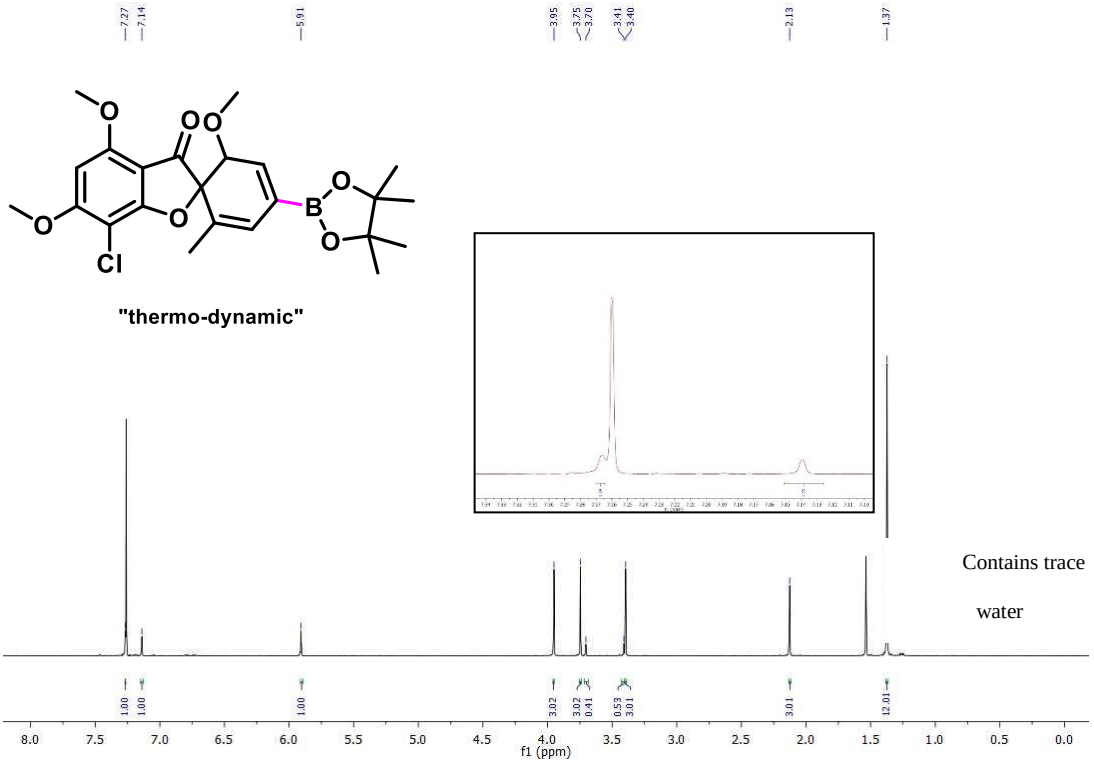

166.17
155.25
154.37
135.83
132.47
130.71
122.84
122.35
84.28
61.42
25.06
14.49
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

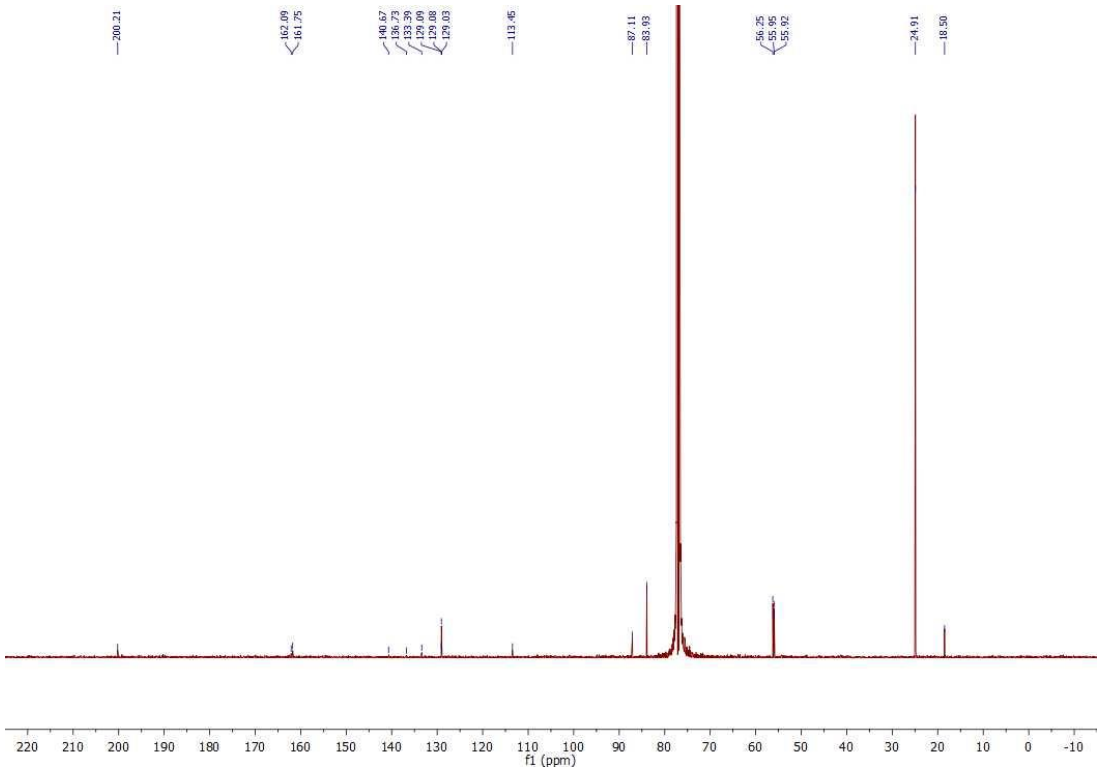


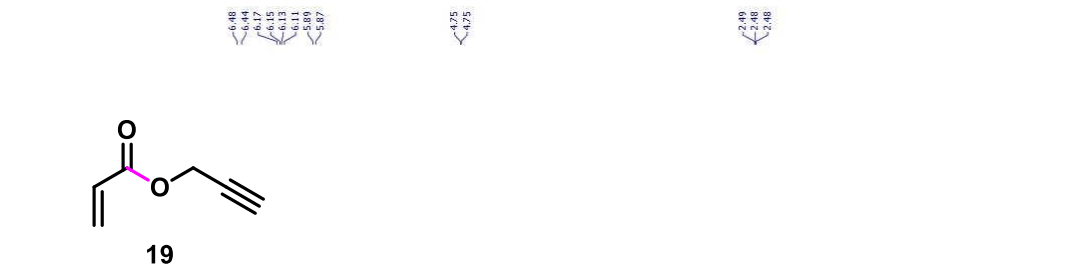
"kinetic"

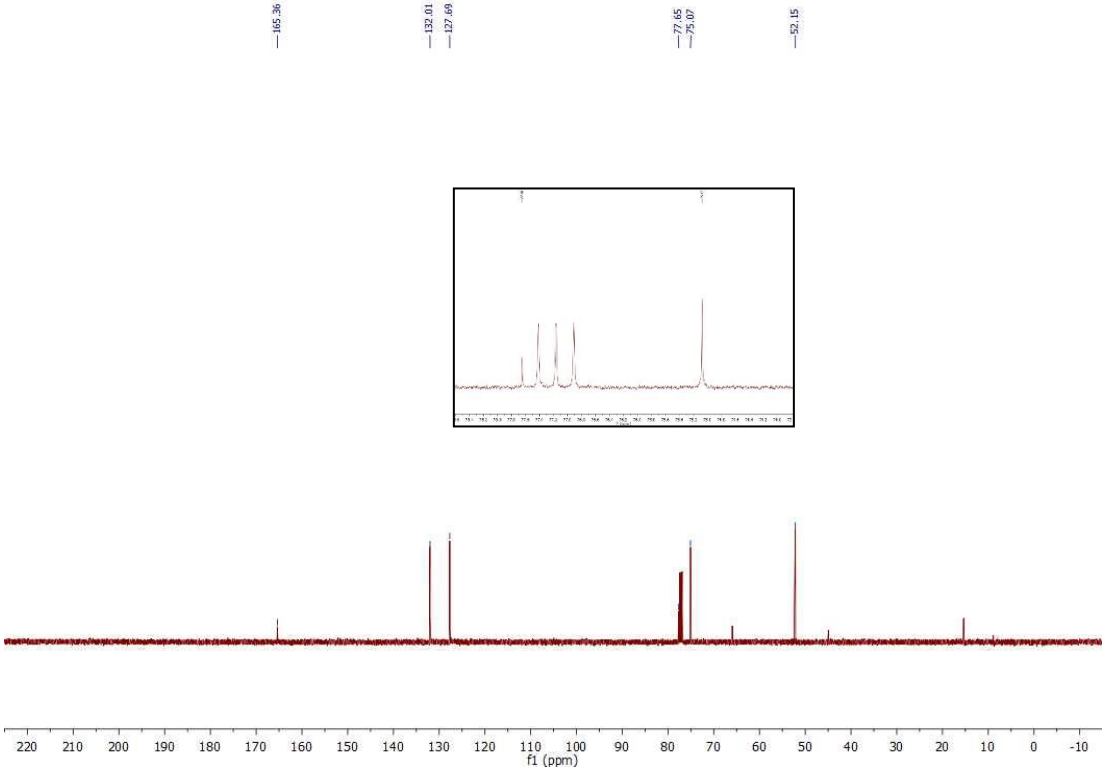


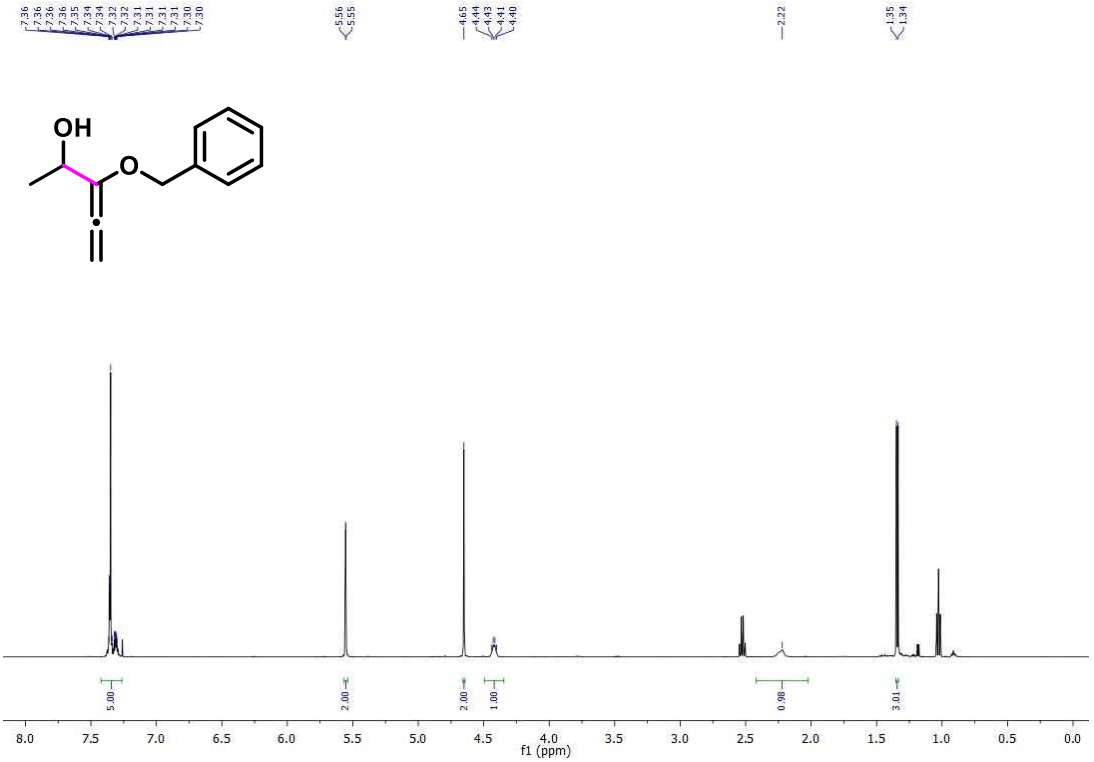


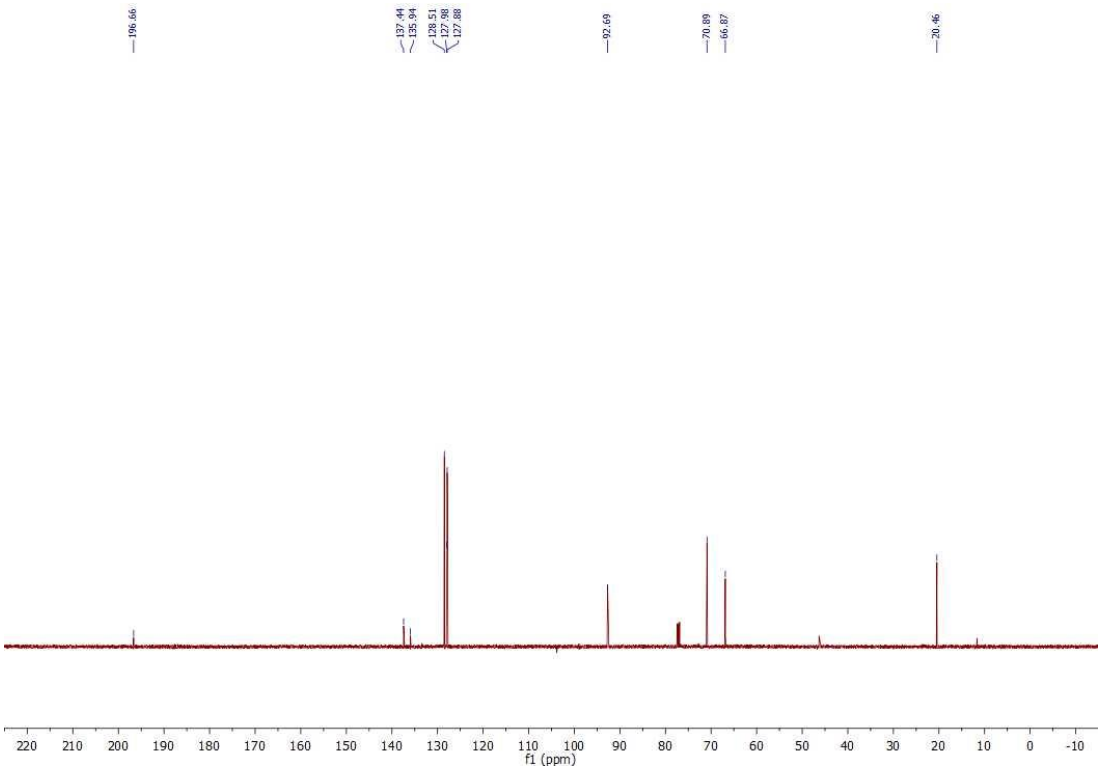

"thermo-dynamic"
Contains trace
water
f1 (ppm)

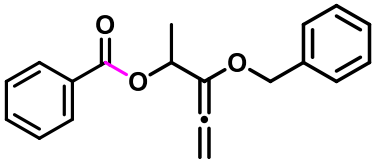

f1 (ppm)

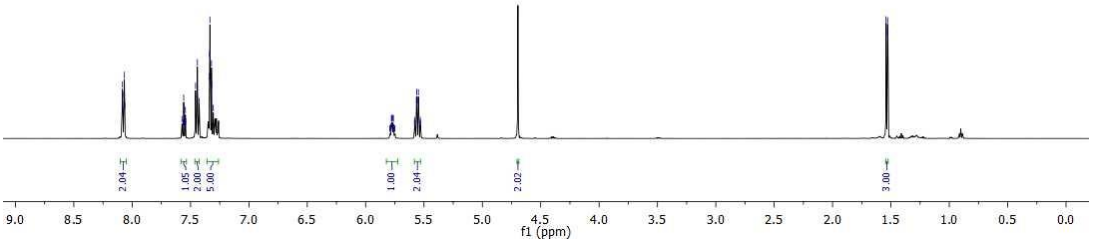

6.48
6.44
6.17
6.15
6.13
6.11
5.89
5.87
4.75
4.75
2.49
2.48
2.48
O
O
19
Contains trace ether
1.00
1.00
1.00
2.00
0.93
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

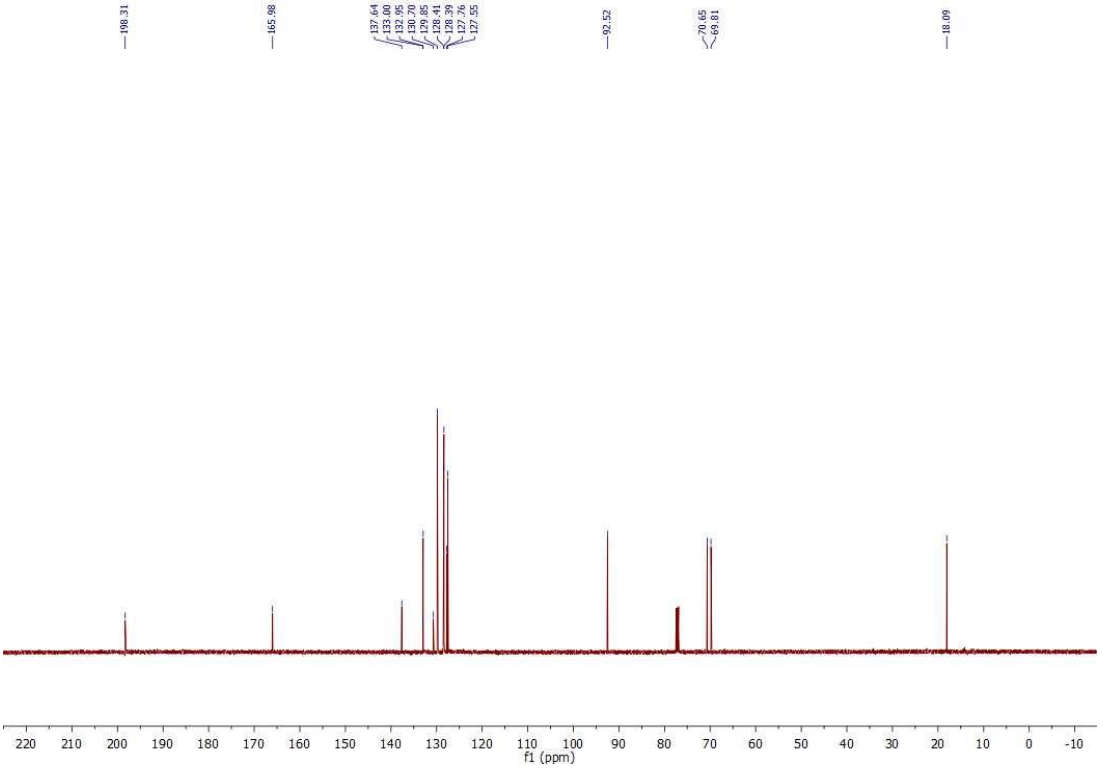

165.36
132.01
127.69
77.65
75.07
52.15
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

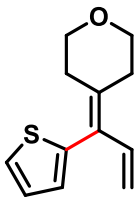

OH
O
f1 (ppm)


f1 (ppm)

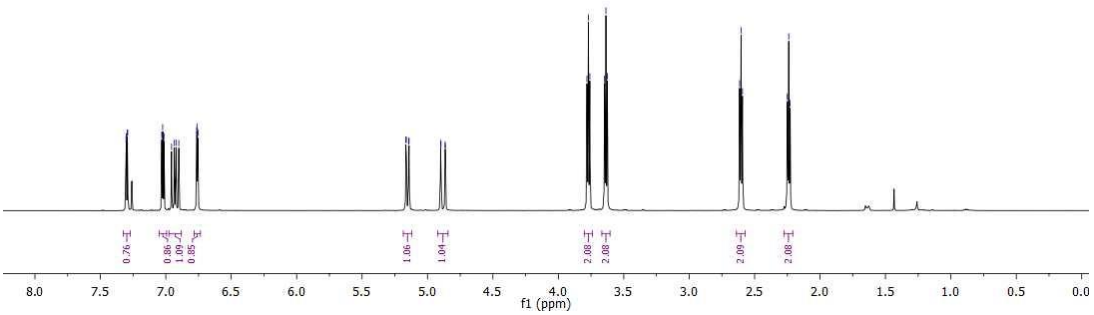


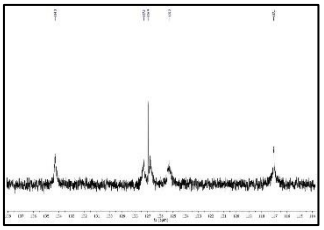

2.04
1.05
2.00
5.00
1.00
2.04
2.02
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

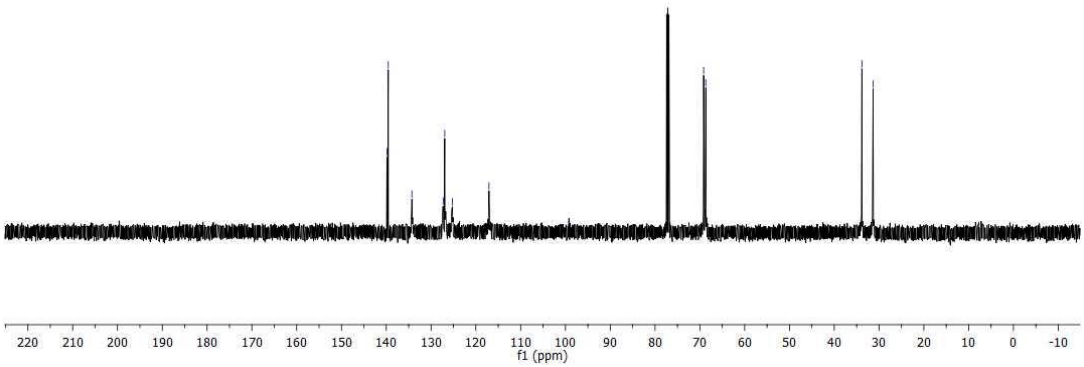

198.31
165.98
137.64
133.00
132.95
130.70
129.85
128.41
128.39
127.76
127.55
92.52
70.65
69.81
18.09
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

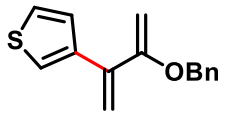


1









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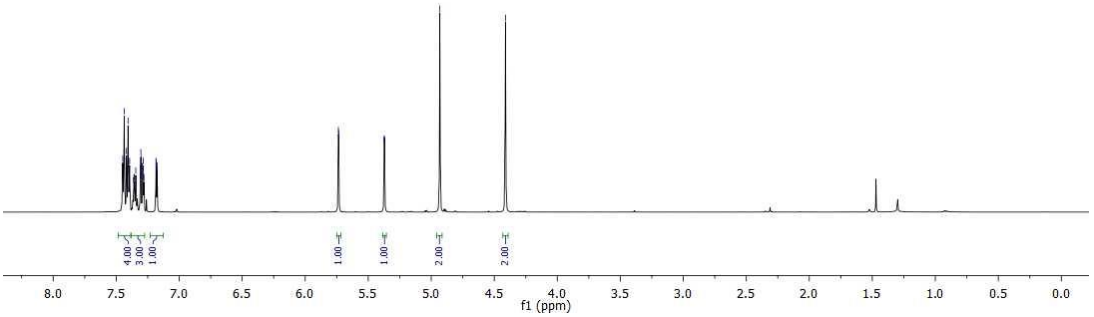
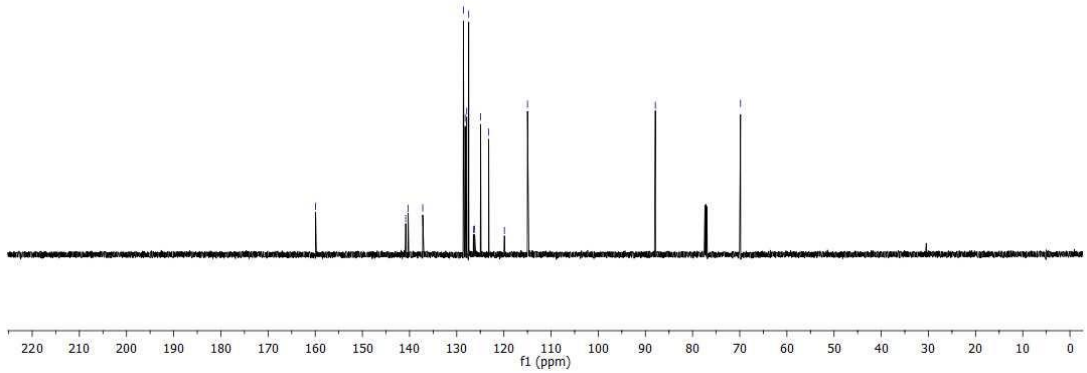
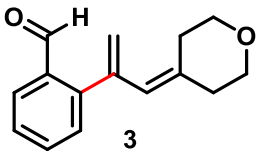
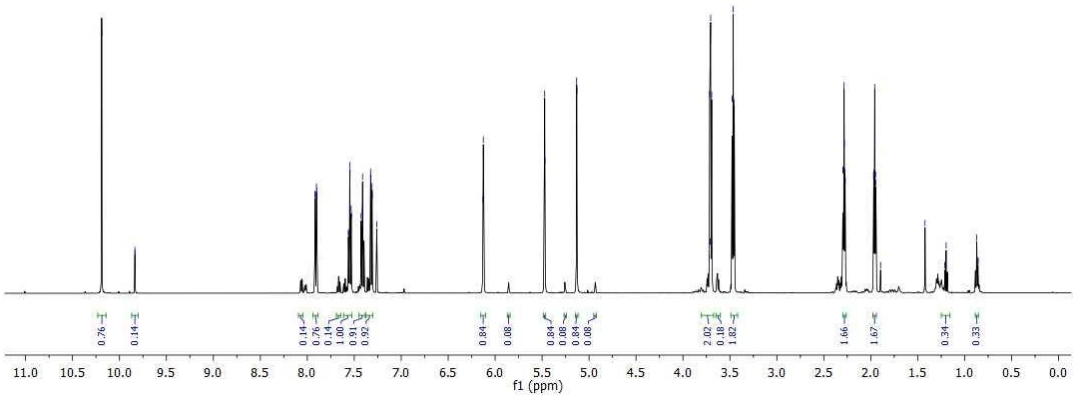
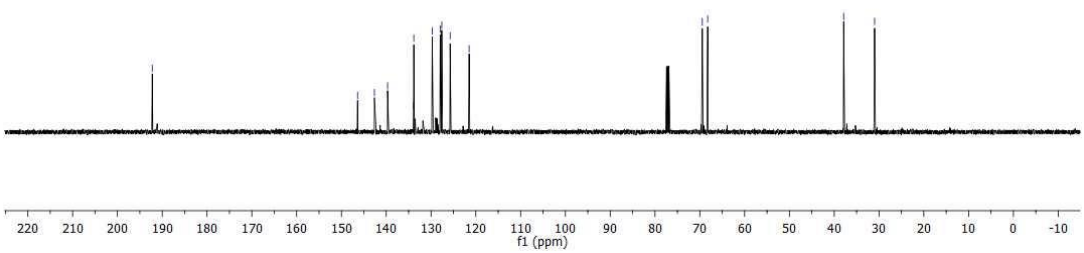


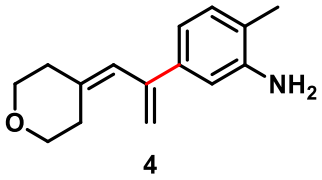




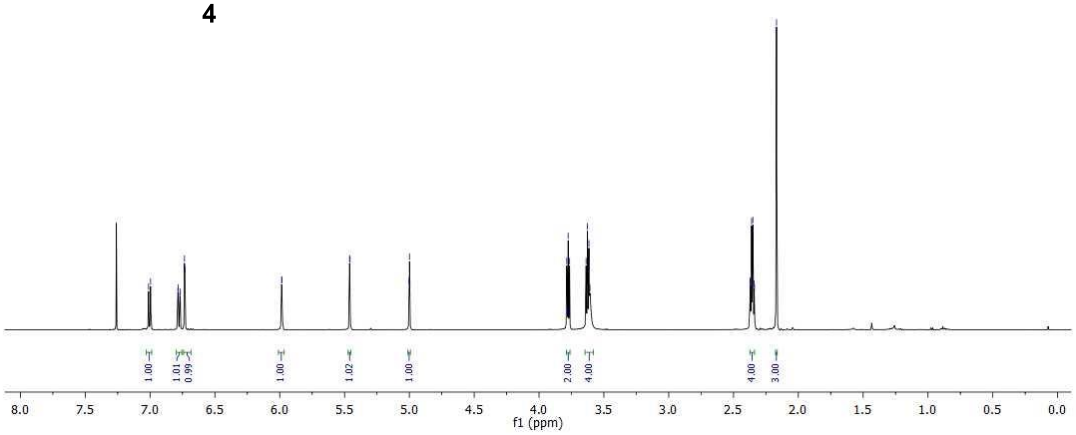
3

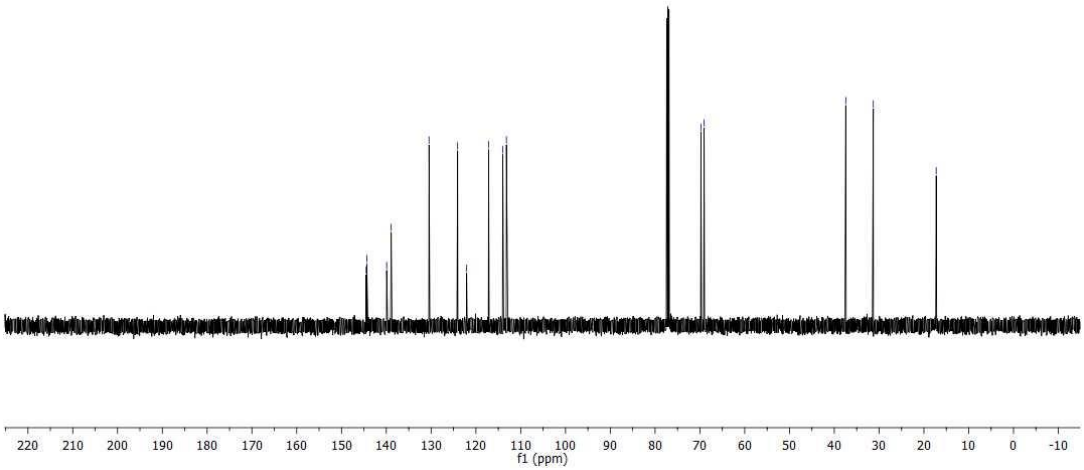


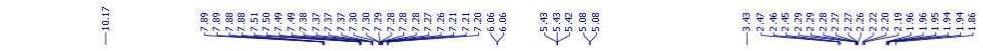


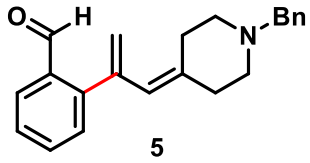


4

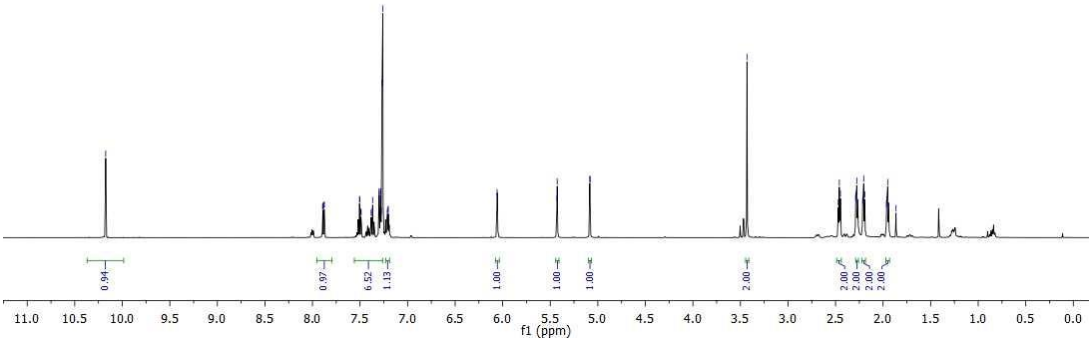


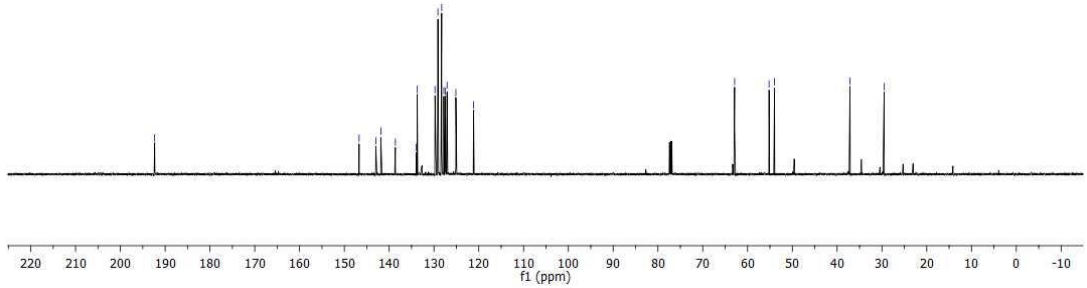


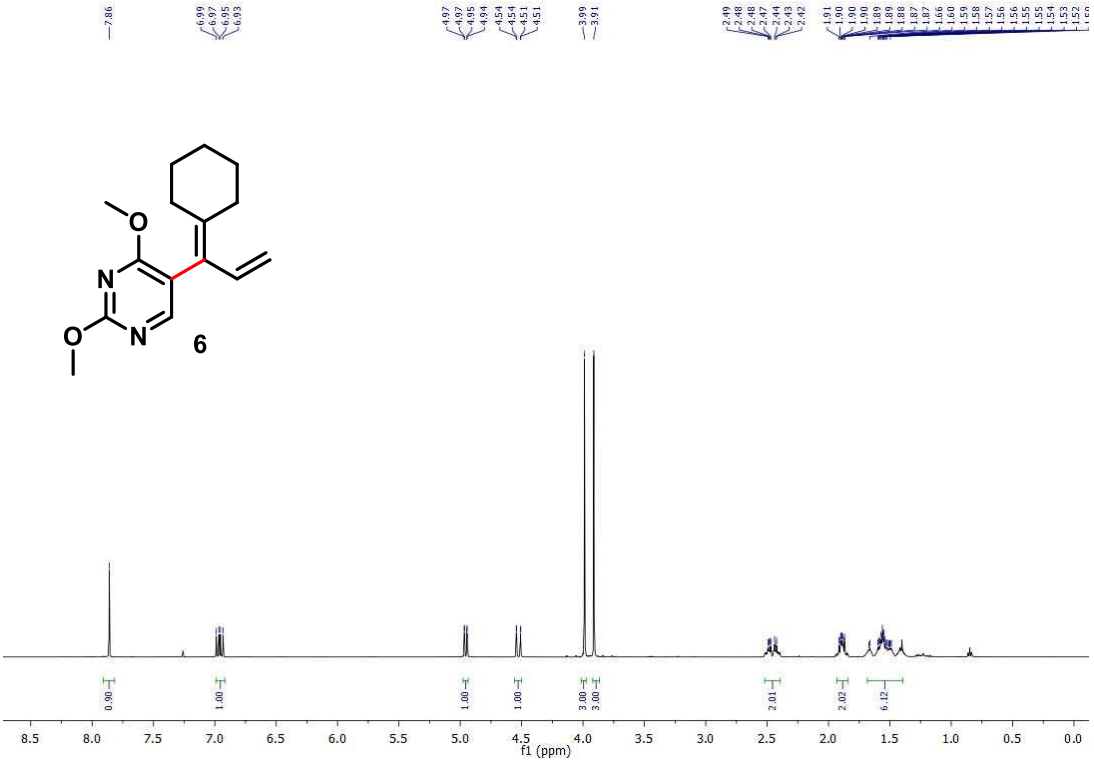



O
H
N
Bn

5


0.94
0.97
6.52
1.13
1.00
1.00
1.00
2.00
2.00
2.00
2.00
2.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.86
6.99
6.97
6.95
6.93
4.97
4.97
4.95
4.94
4.54
4.54
4.51
4.51
3.99
3.91
2.49
2.48
2.48
2.47
2.44
2.43
2.42
1.91
1.90
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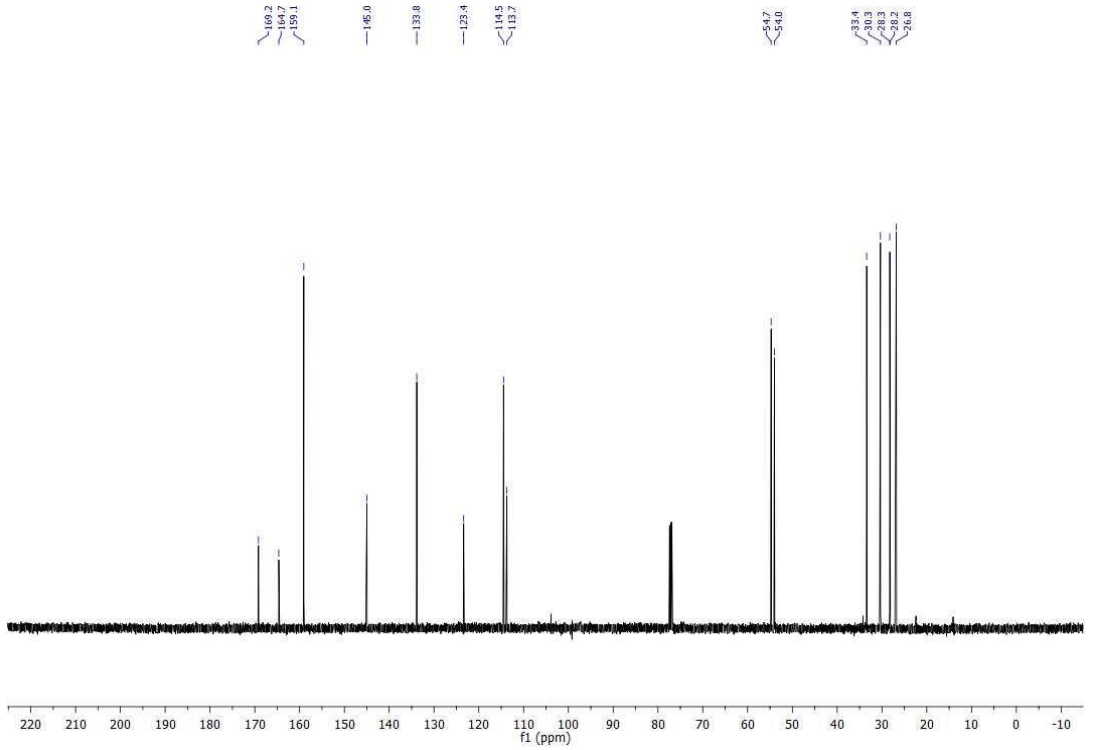
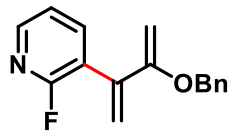
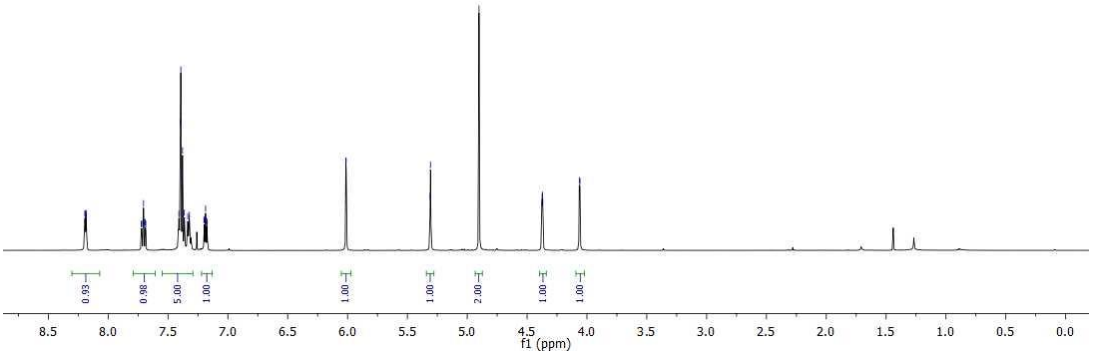
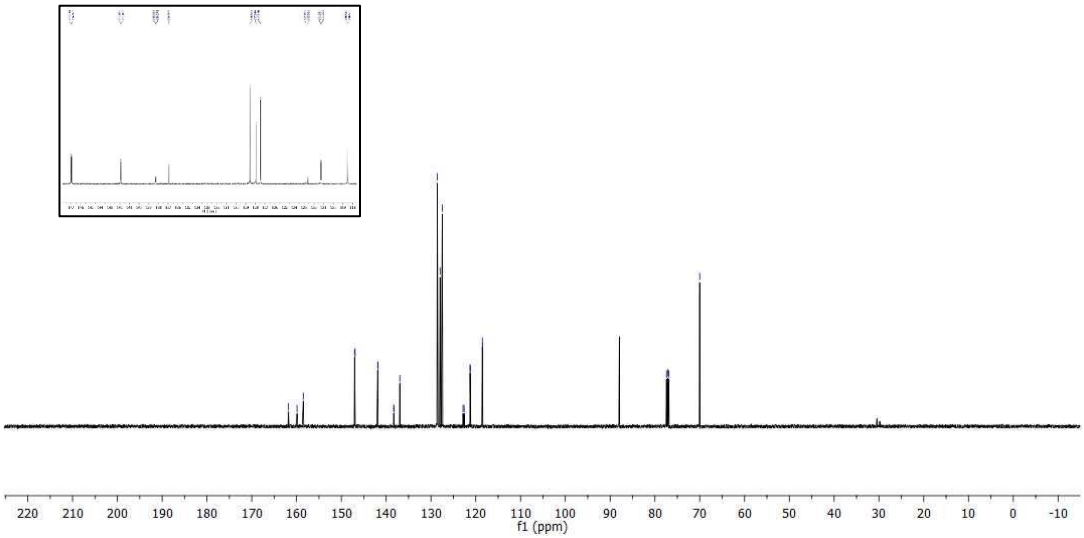
1.88
1.87
1.87
1.66
1.60
1.59
1.58
1.57
1.56
1.56
1.55
1.55
1.54
1.53
1.52
O
N
N
O
6
0.90
1.00
1.00
1.00
3.00
3.00
2.01
2.02
6.12
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

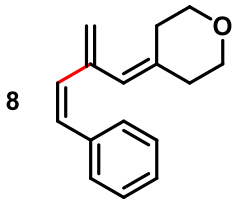

160.2
164.7
159.1
146.0
133.8
123.4
114.5
113.7
54.7
54.0
33.4
30.3
28.3
28.2
26.8
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



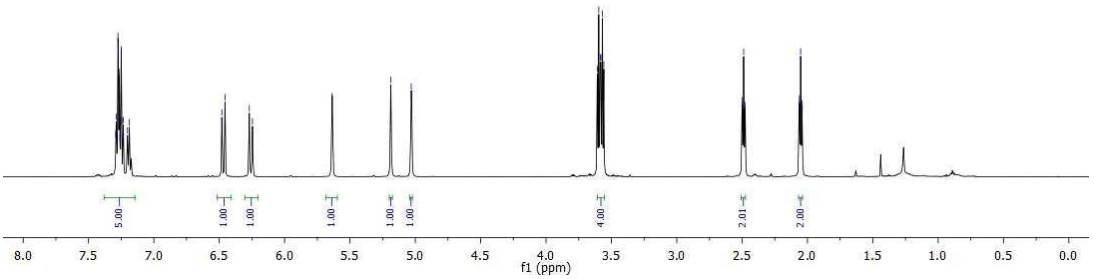
7

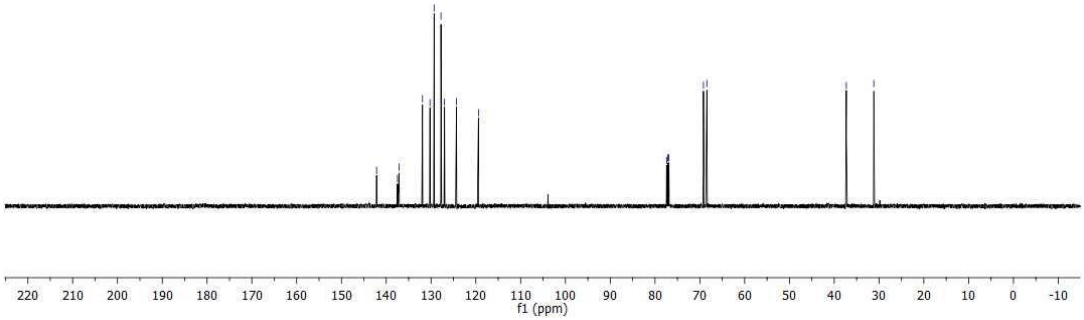


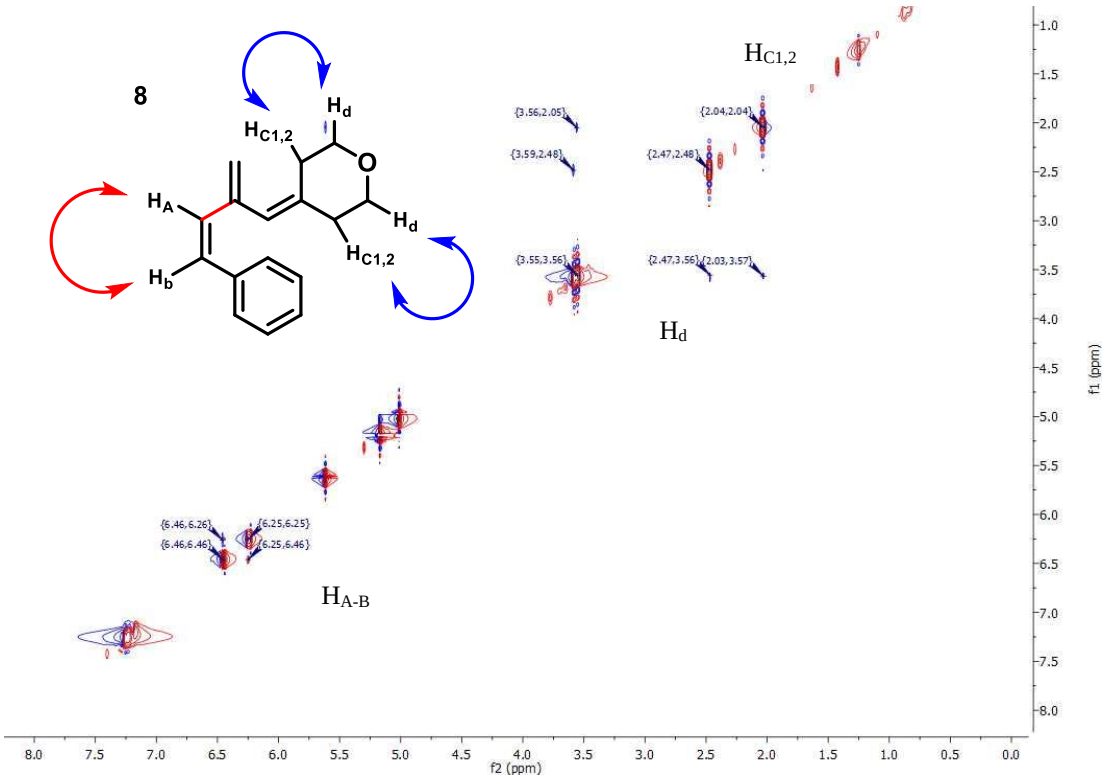


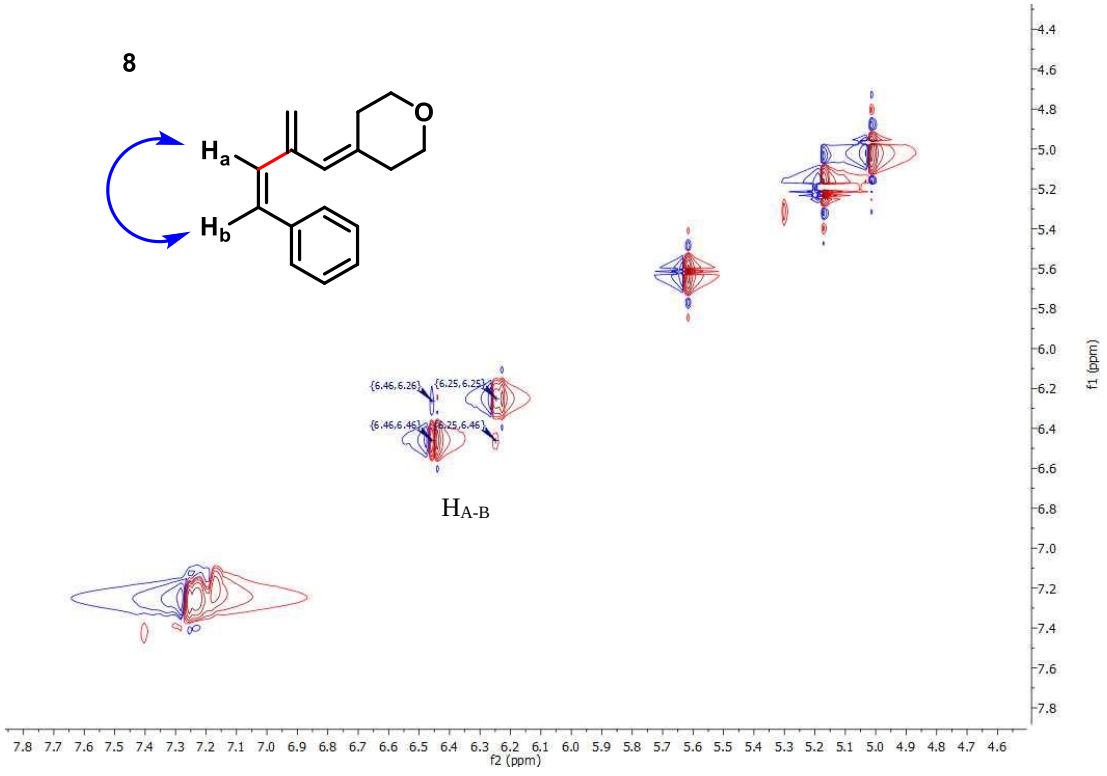


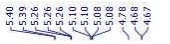
8

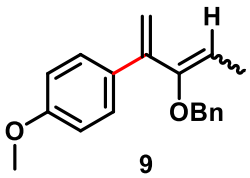




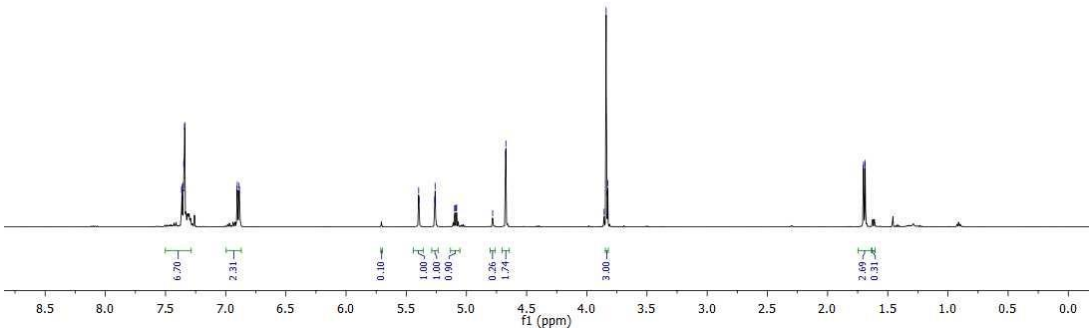

8
H_d
$H_{C1,2}$
O
H_A
H_d
H_b
$H_{C1,2}$
$H_{C1,2}$
H_d
H_{A-B}
f2 (ppm)
f1 (ppm)

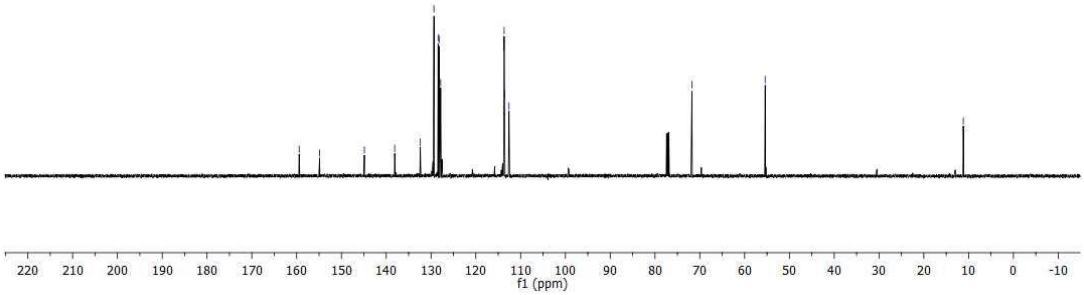

8
H_a
O
H_b
H_{A-B}
f2 (ppm)
f1 (ppm)

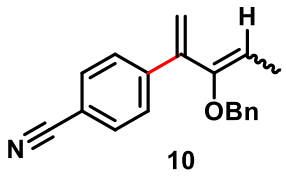



H
OBn
O

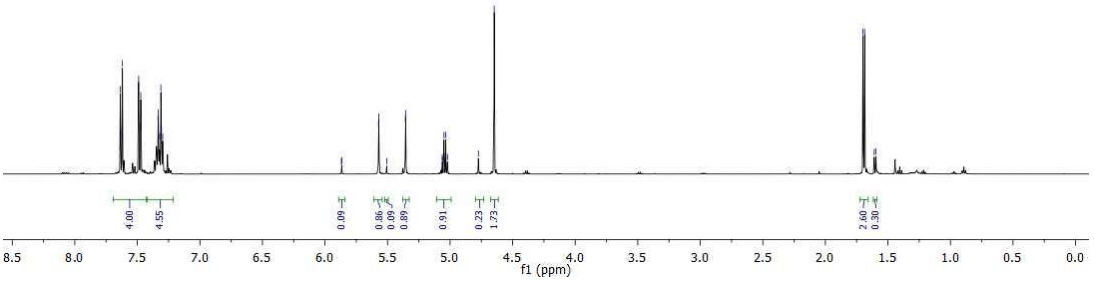
9

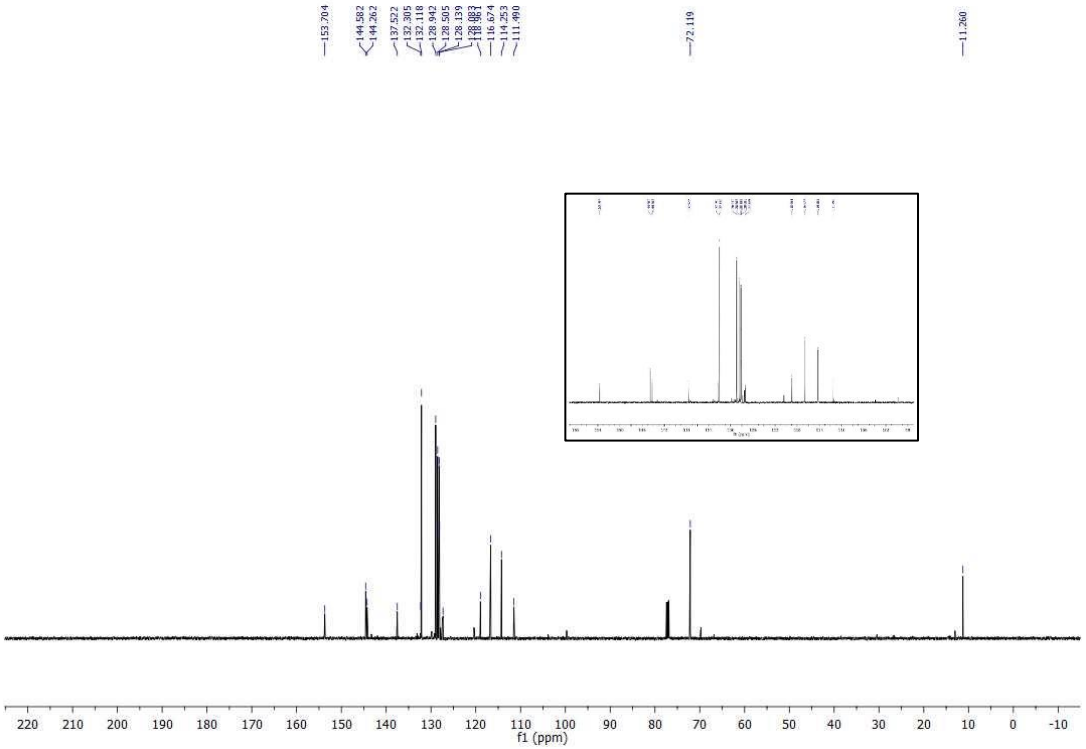

6.70
2.31
0.10
1.00
1.00
0.90
0.26
1.74
3.00
2.69
0.31
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

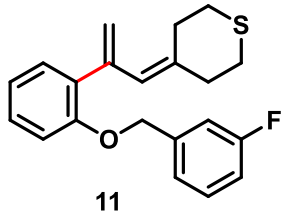

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H
OBn
N

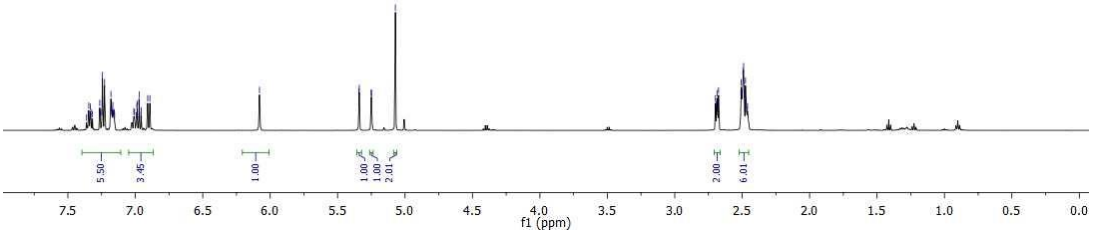
10

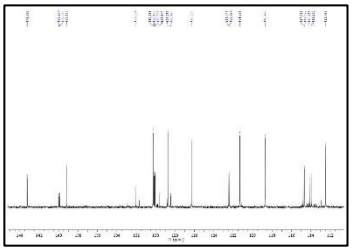

4.00
4.55
0.09
0.86
0.09
0.89
0.91
0.23
1.73
2.60
0.30
f1 (ppm)

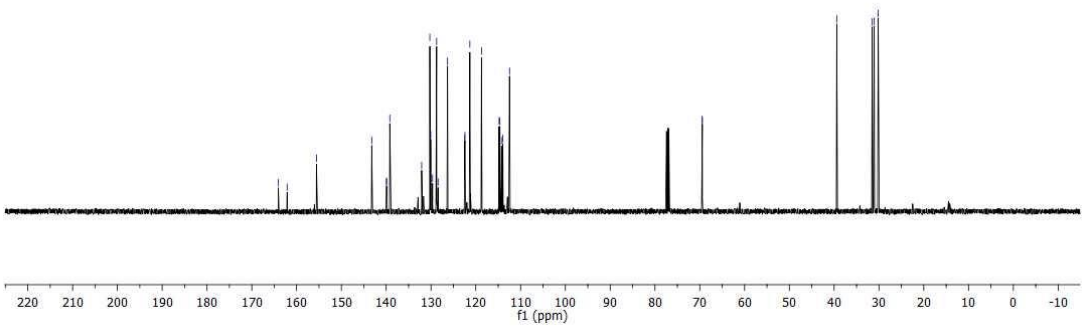

153.704
144.582
144.262
137.522
132.395
132.110
128.942
128.505
128.139
116.674
114.253
111.490
72.119
11.260
f1 (ppm)

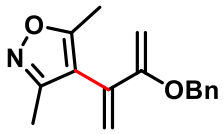

S
F
O

11

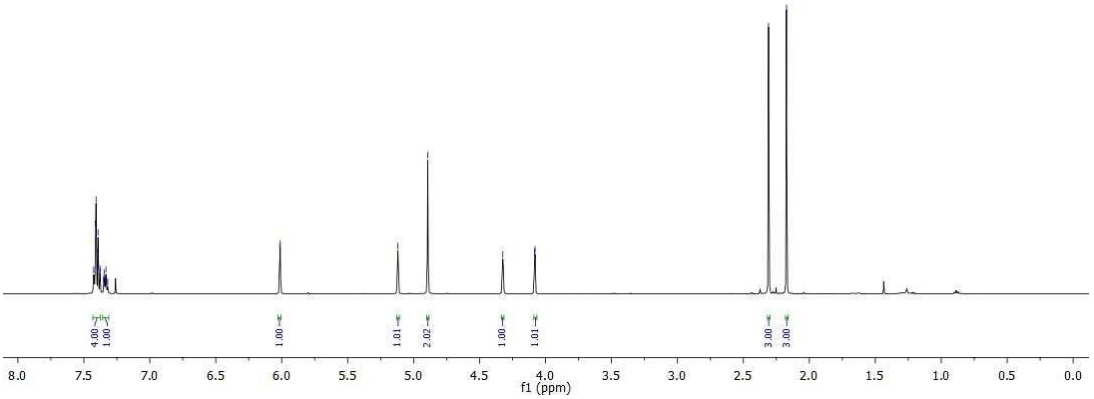

5.50
3.45
1.00
1.00
1.00
2.01
2.00
6.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

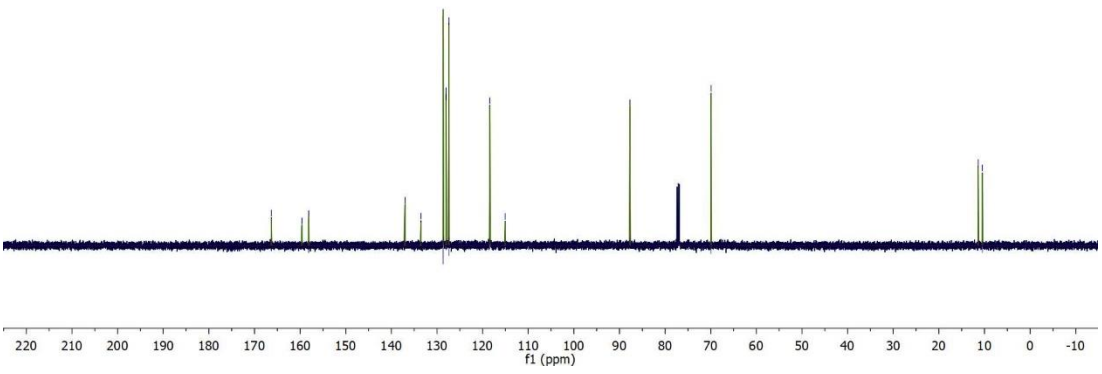


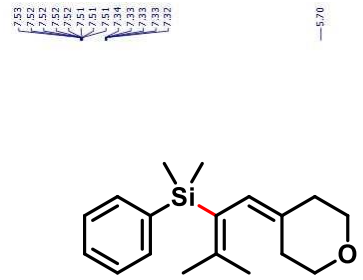

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



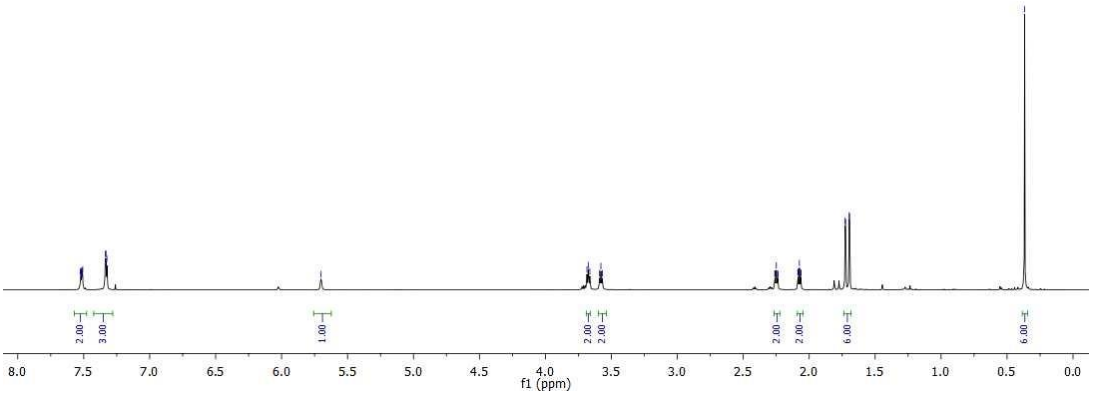
12

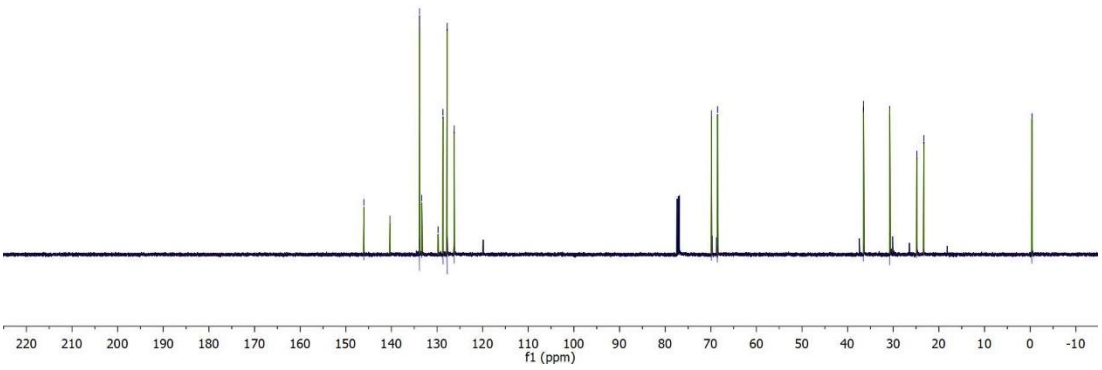


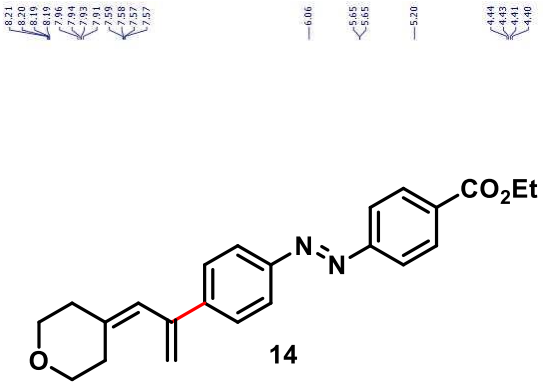


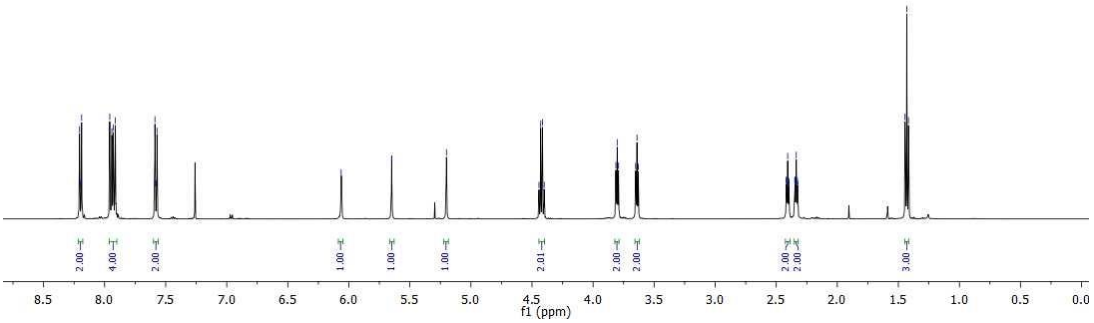


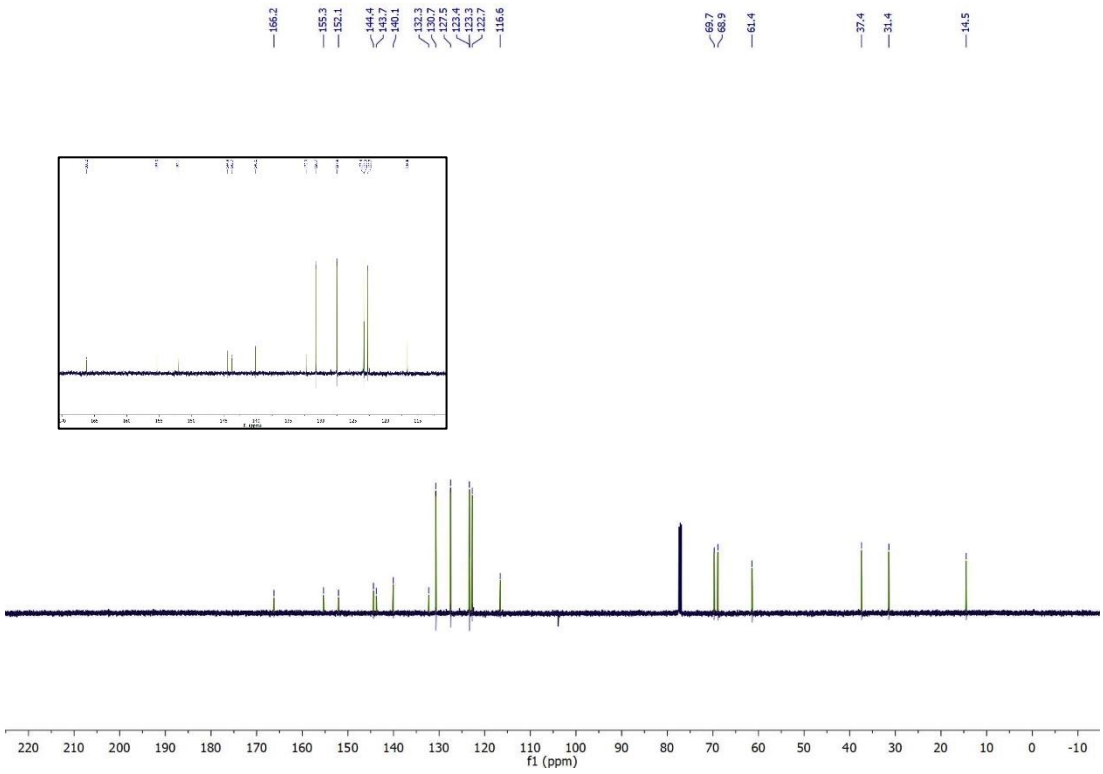
13

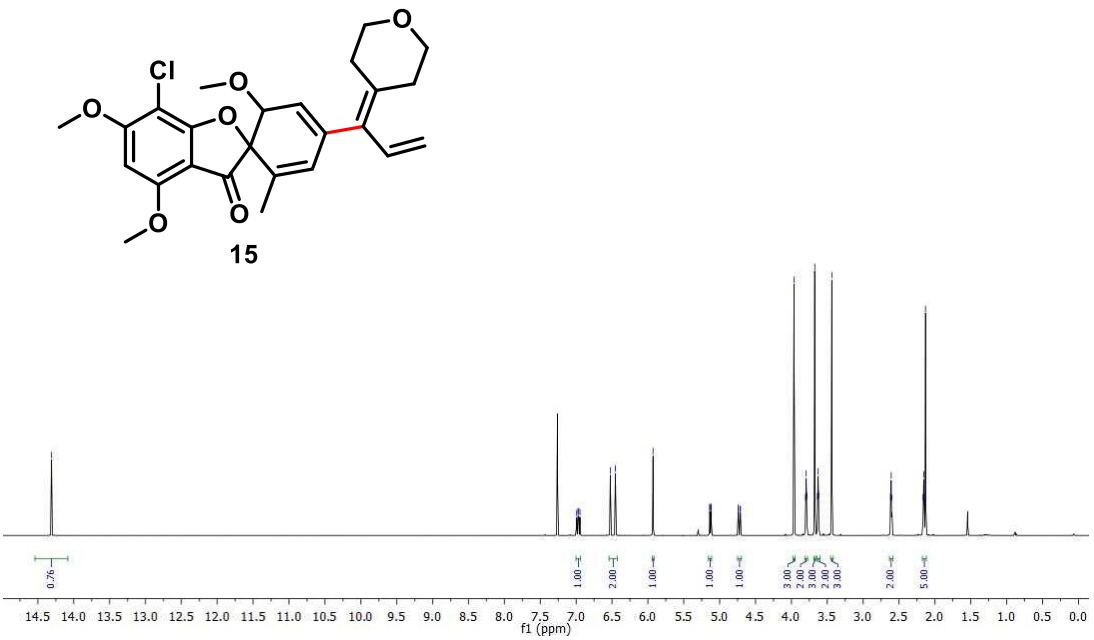


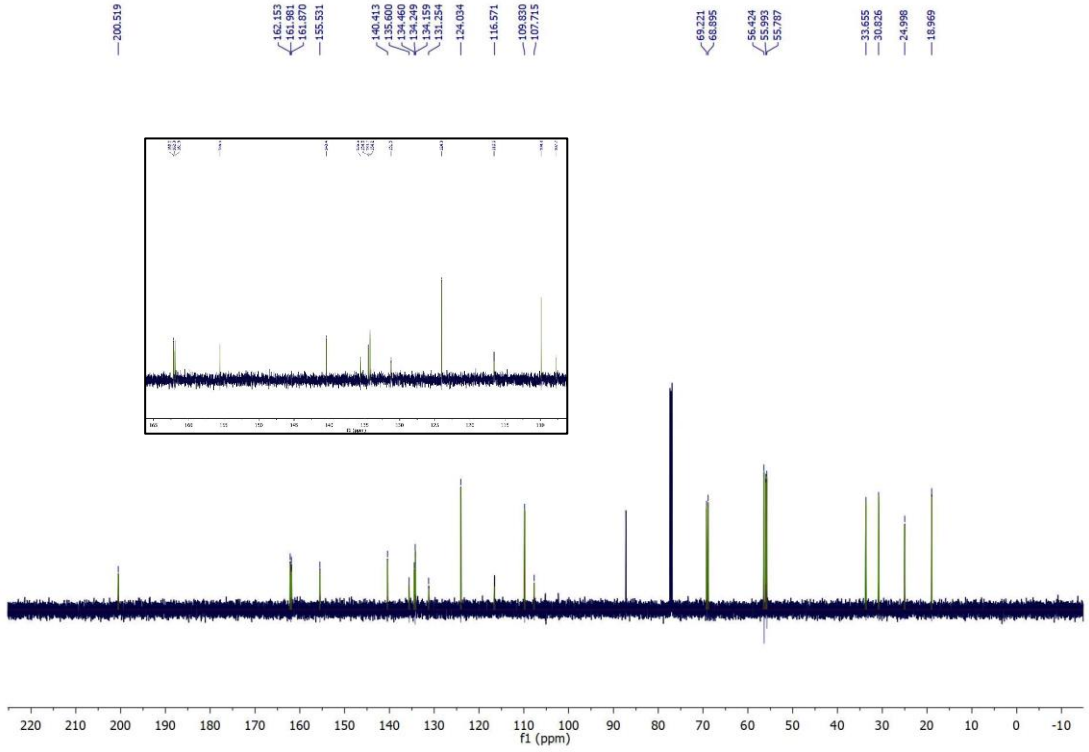



CO2Et
N
N
O
14


f1 (ppm)

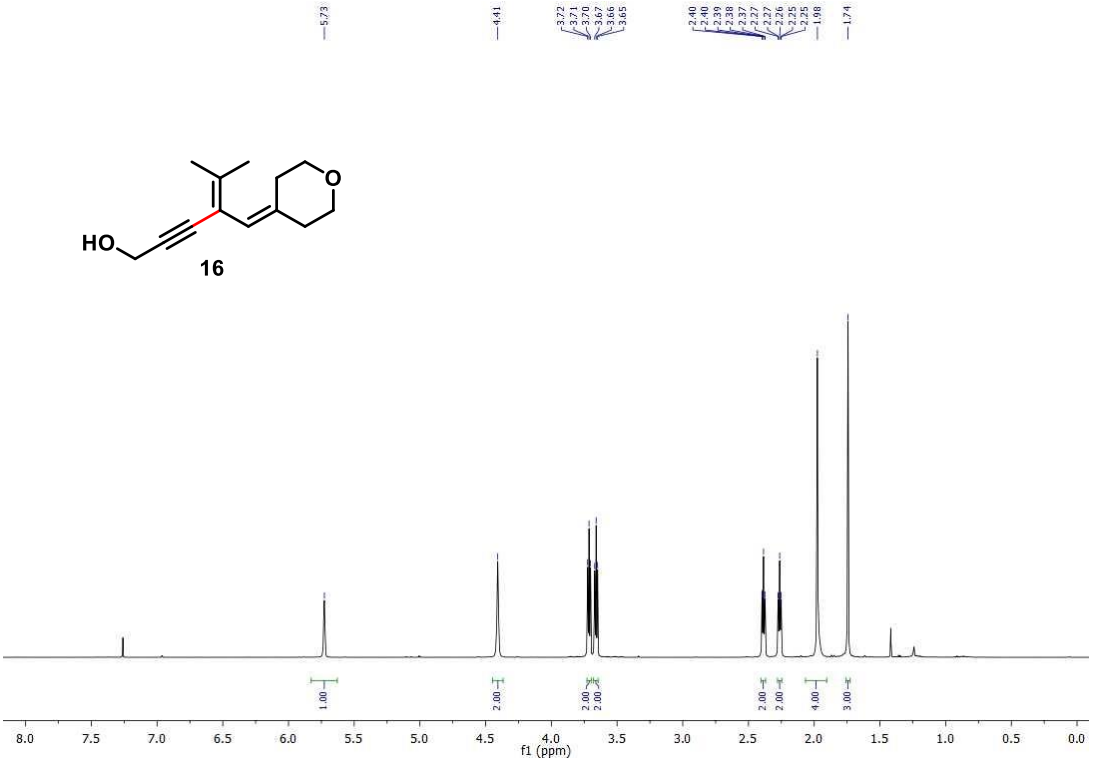

f1 (ppm)

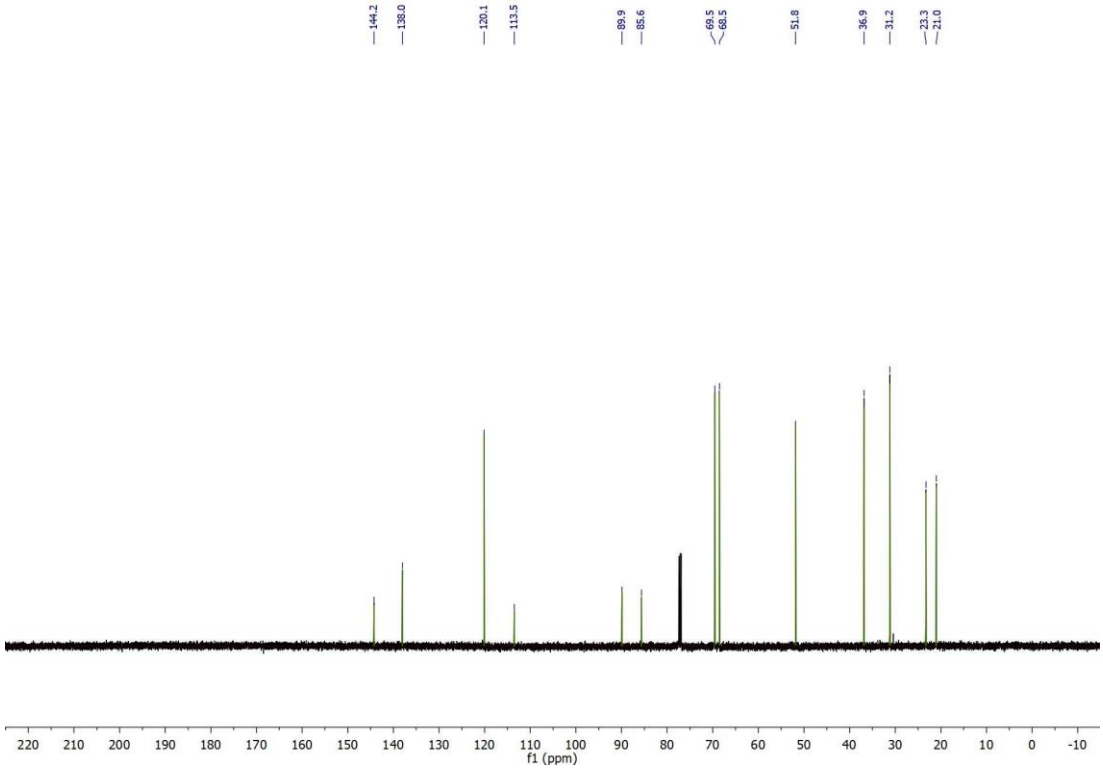

14.31
6.99
6.97
6.96
6.95
6.52
6.45
5.93
5.14
5.14
5.12
5.12
4.74
4.74
4.71
4.71
3.96
3.80
3.79
3.79
3.68
3.64
3.63
3.62
3.44
2.62
2.61
2.60
2.16
2.16
2.15
2.13
Cl
O
O
O
O
O
O
15
0.76
1.00
2.00
1.00
1.00
1.00
3.00
2.00
3.00
2.00
3.00
2.00
5.00
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

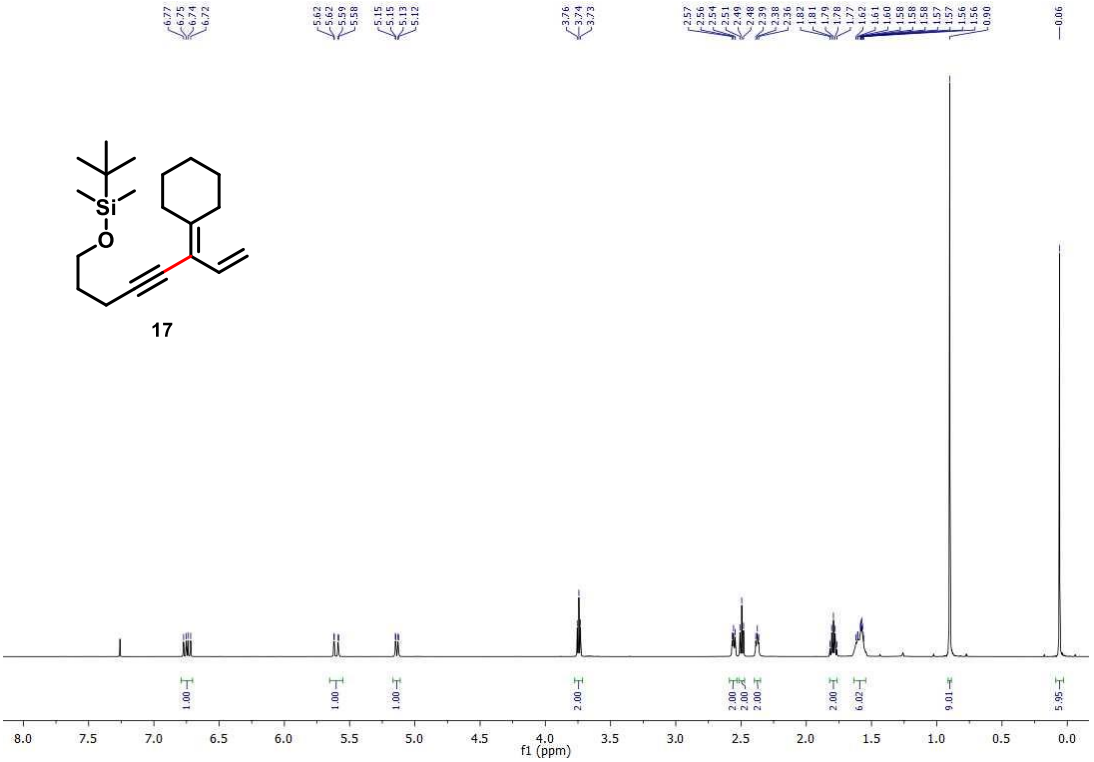

200.519
162.153
161.981
161.670
155.531
140.413
135.600
134.460
134.249
134.159
131.254
124.034
116.571
109.830
107.715
69.221
68.895
56.424
55.993
55.787
33.655
30.826
24.998
18.969
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

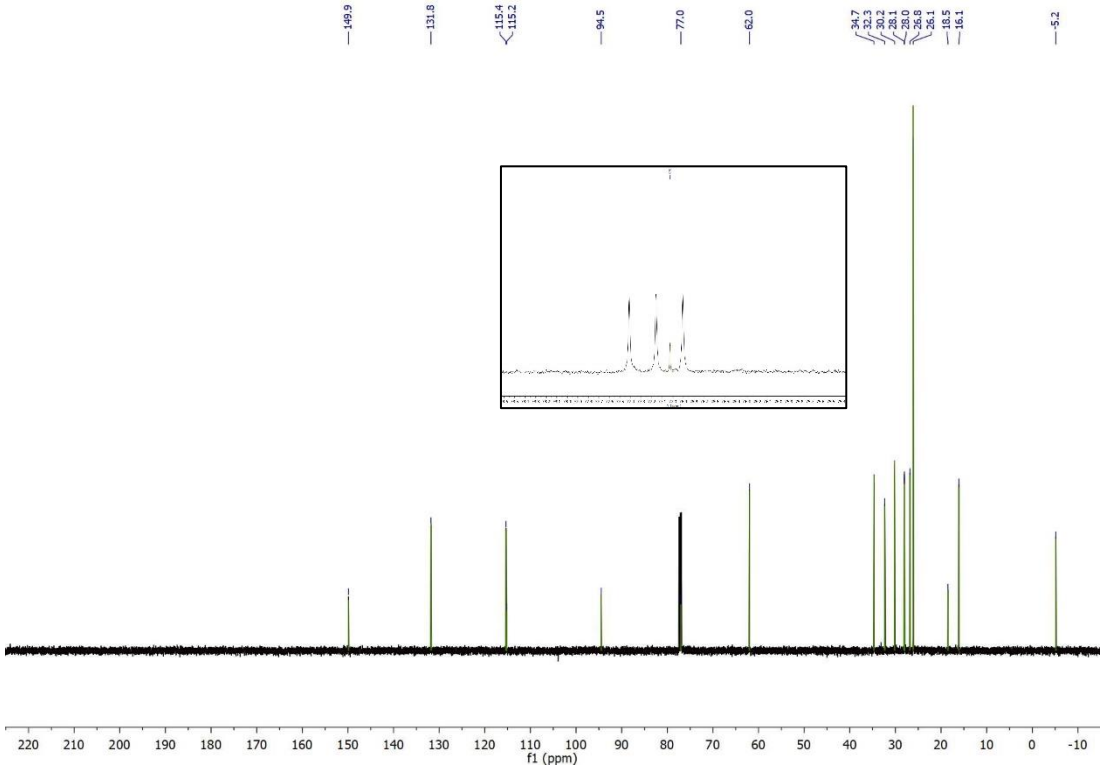
HO
O

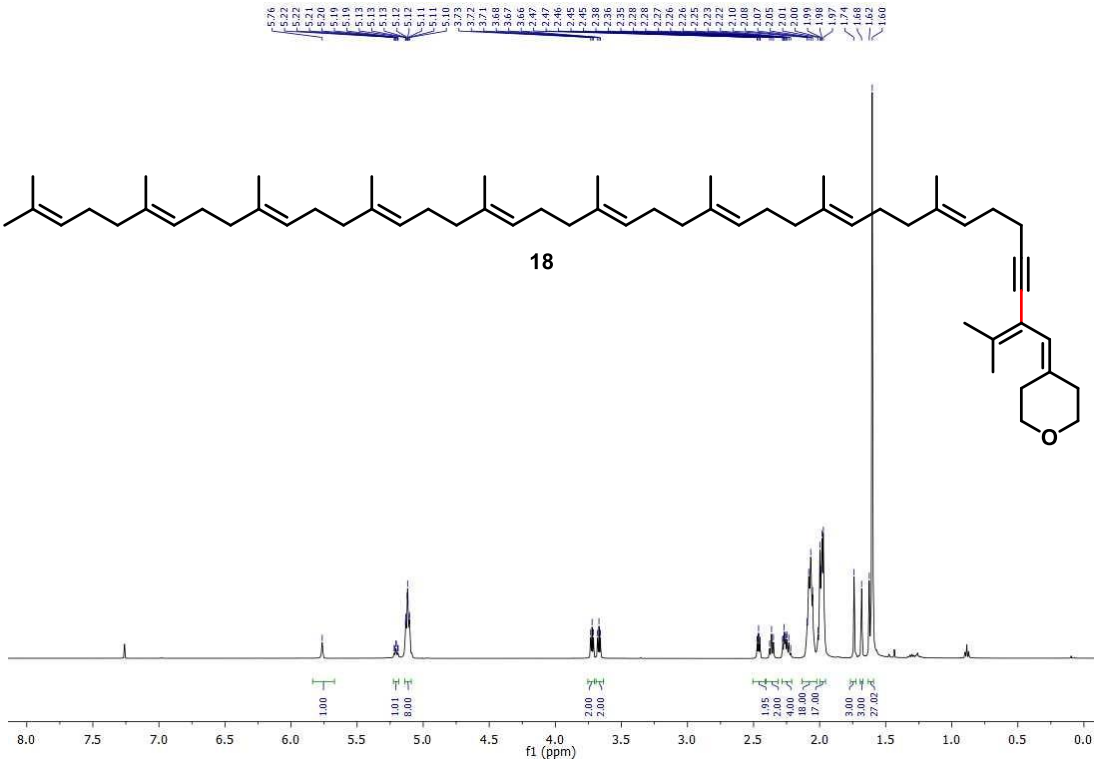
16

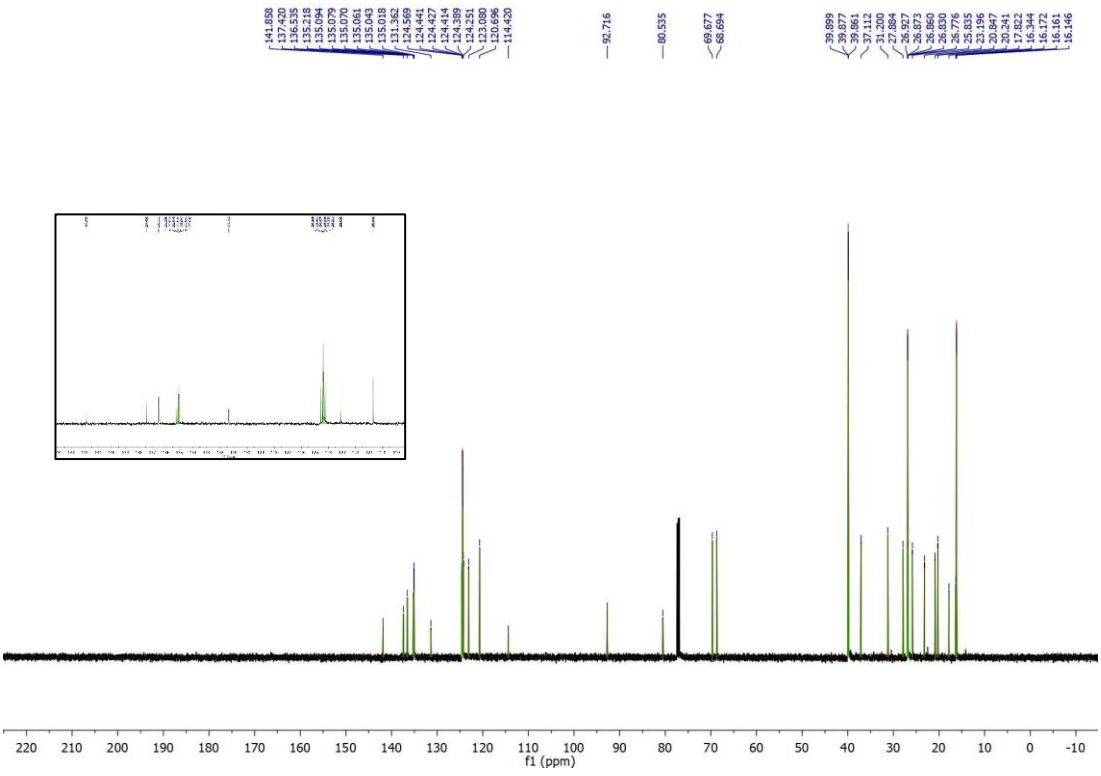

5.73
4.41
3.72
3.71
3.70
3.67
3.66
3.65
2.40
2.40
2.39
2.38
2.37
2.27
2.27
2.26
2.25
2.25
1.98
1.74
1.00
2.00
2.00
2.00
2.00
4.00
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

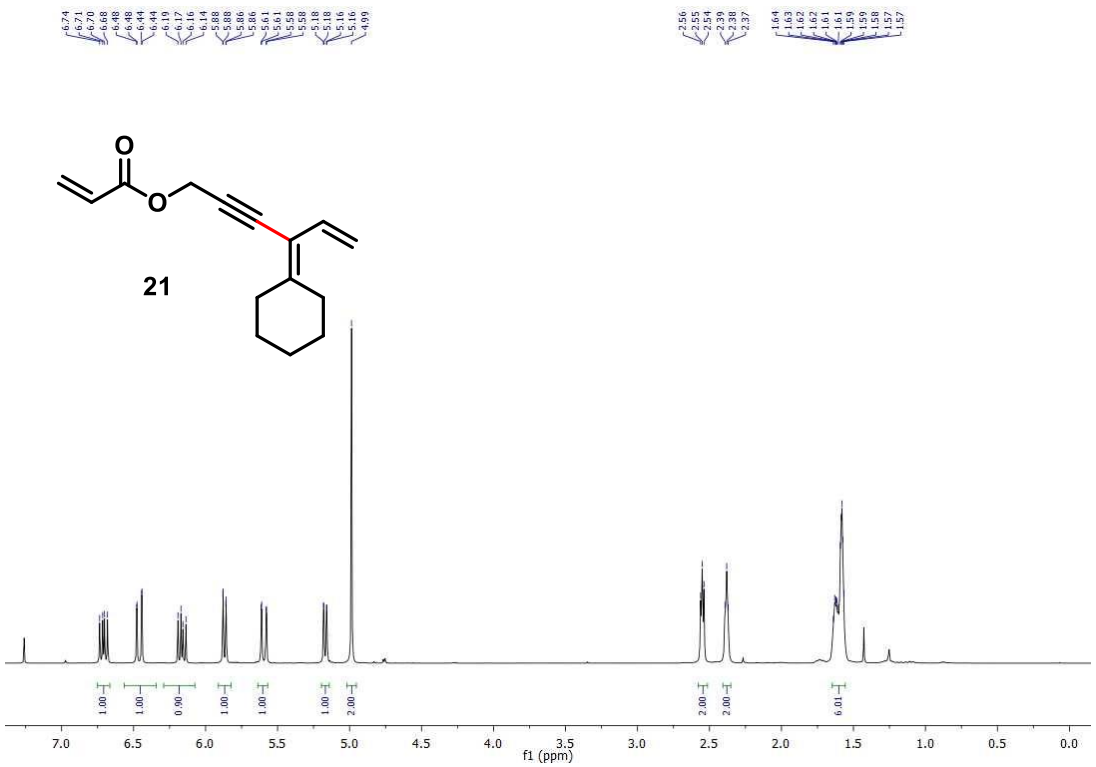

144.2
138.0
120.1
113.5
89.9
85.6
69.5
68.5
51.8
36.9
31.2
23.3
21.0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

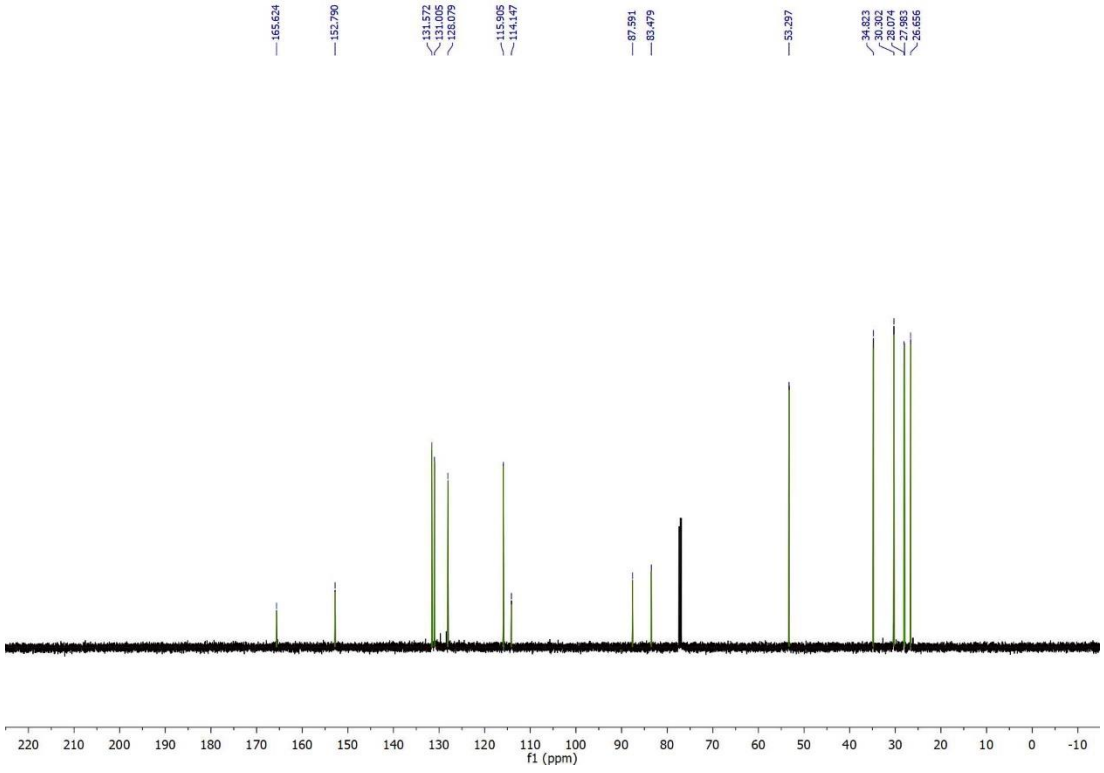

Si
O
17
f1 (ppm)

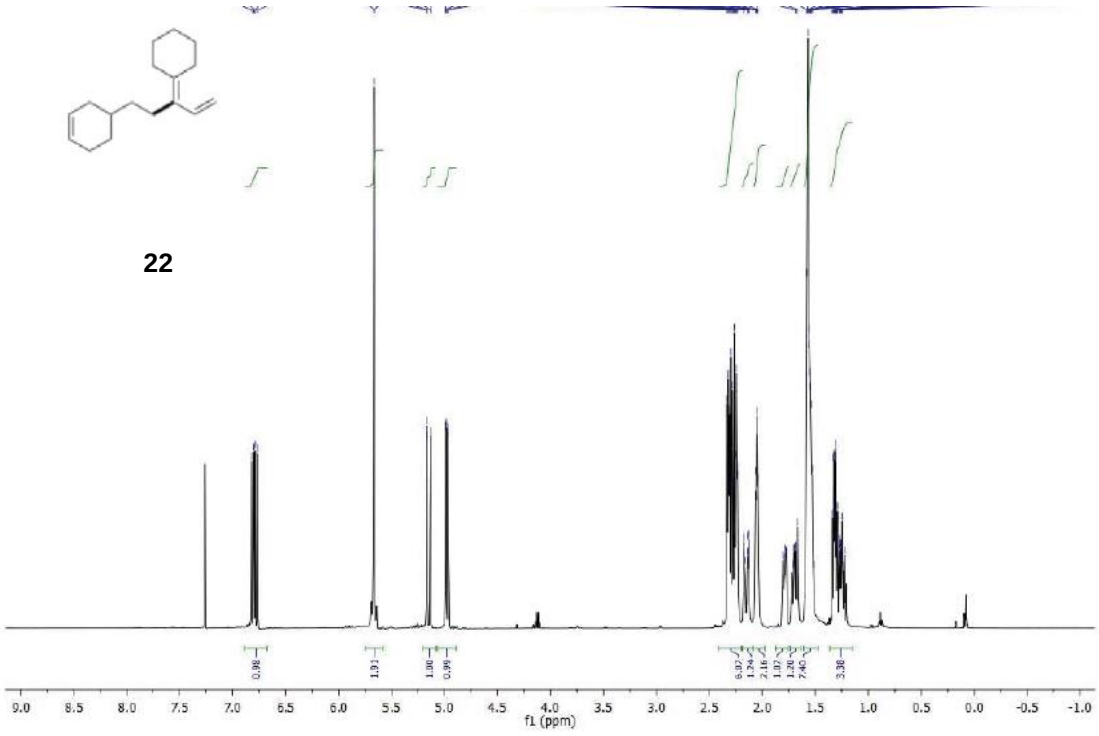

f1 (ppm)


18
f1 (ppm)

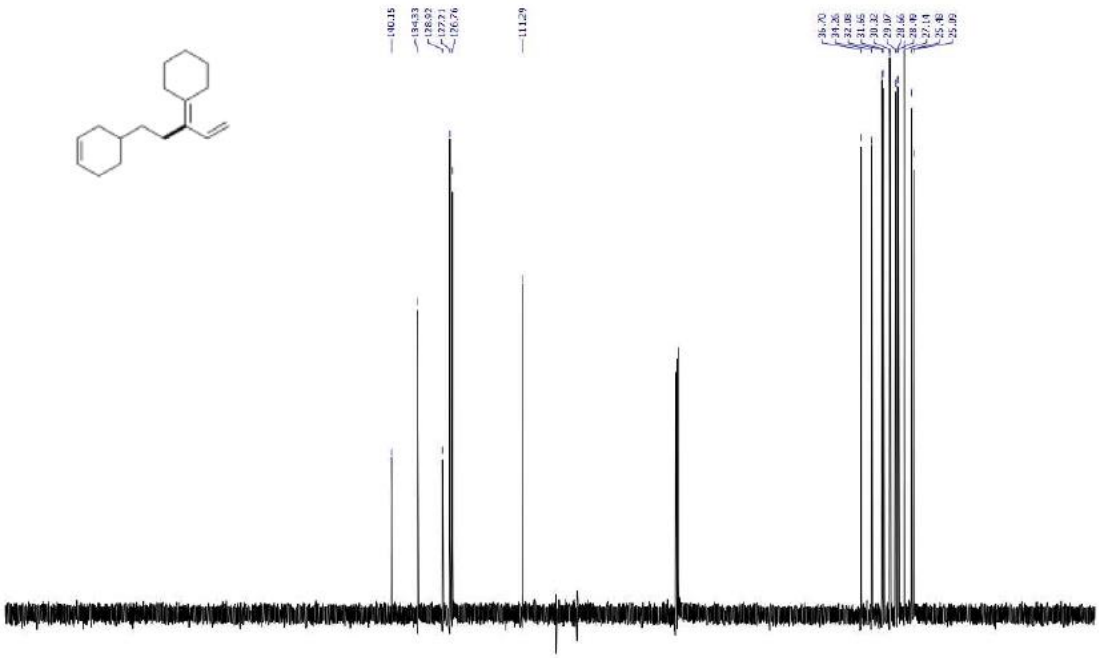

f1 (ppm)

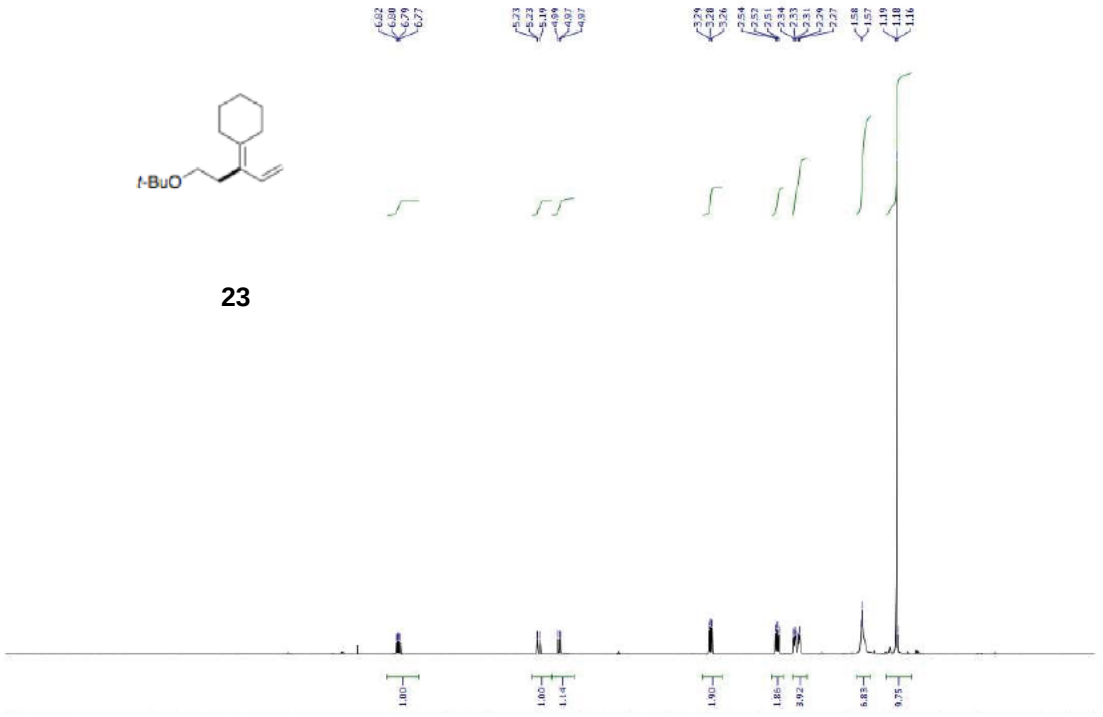

21
f1 (ppm)


f1 (ppm)

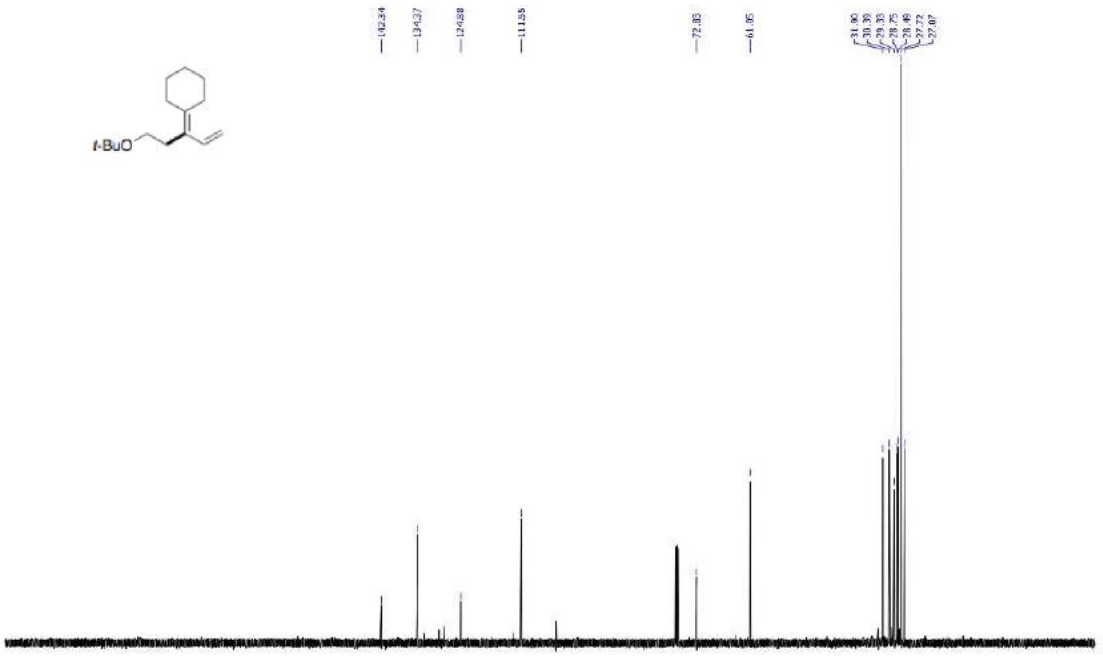


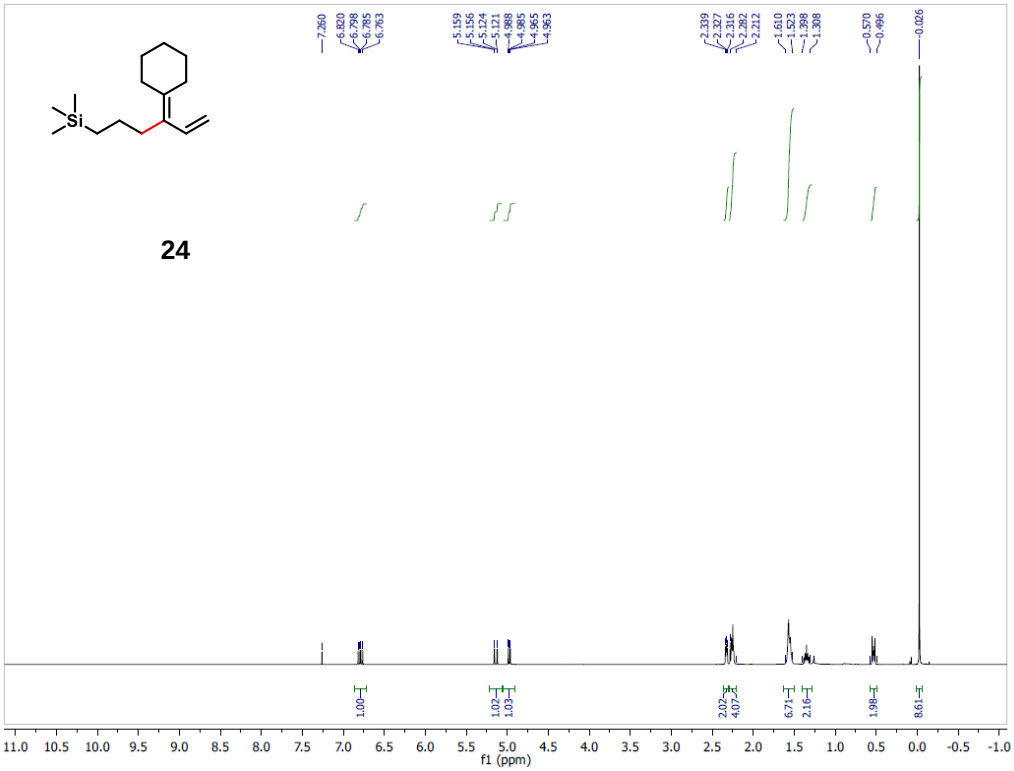
22




t-BuO
6.02
6.00
5.79
5.77
5.33
5.23
5.19
4.99
4.97
4.97
3.29
3.28
3.26
2.54
2.53
2.51
2.34
2.33
2.31
2.29
2.27
1.58
1.57
1.19
1.18
1.16
1.00
1.00
1.14
1.90
1.86
3.92
6.83
9.75

23


t-BuO
132.54
134.27
124.88
111.55
72.83
61.05
31.90
30.39
29.33
28.75
28.49
27.72
27.07


Si
7.260
6.820
6.798
6.785
6.763
5.159
5.156
5.124
5.121
4.988
4.985
4.965
4.963
2.339
2.327
2.316
2.282
2.212
1.610
1.523
1.398
1.308
0.570
0.496
0.026
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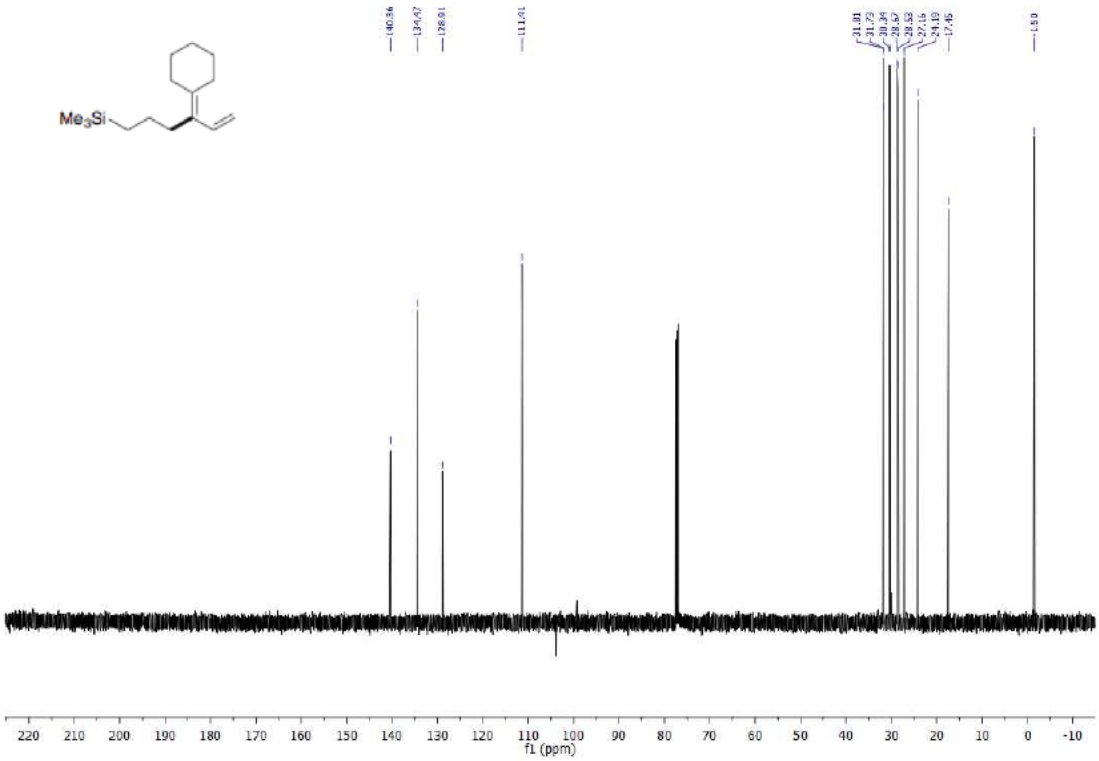
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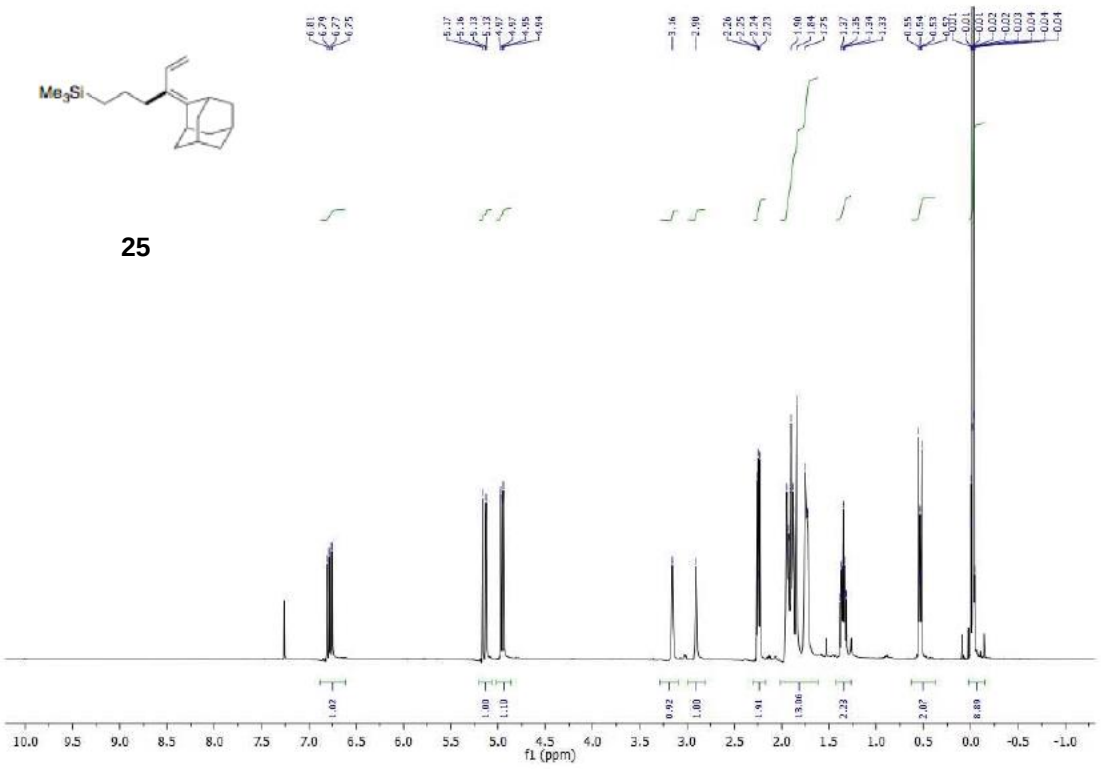

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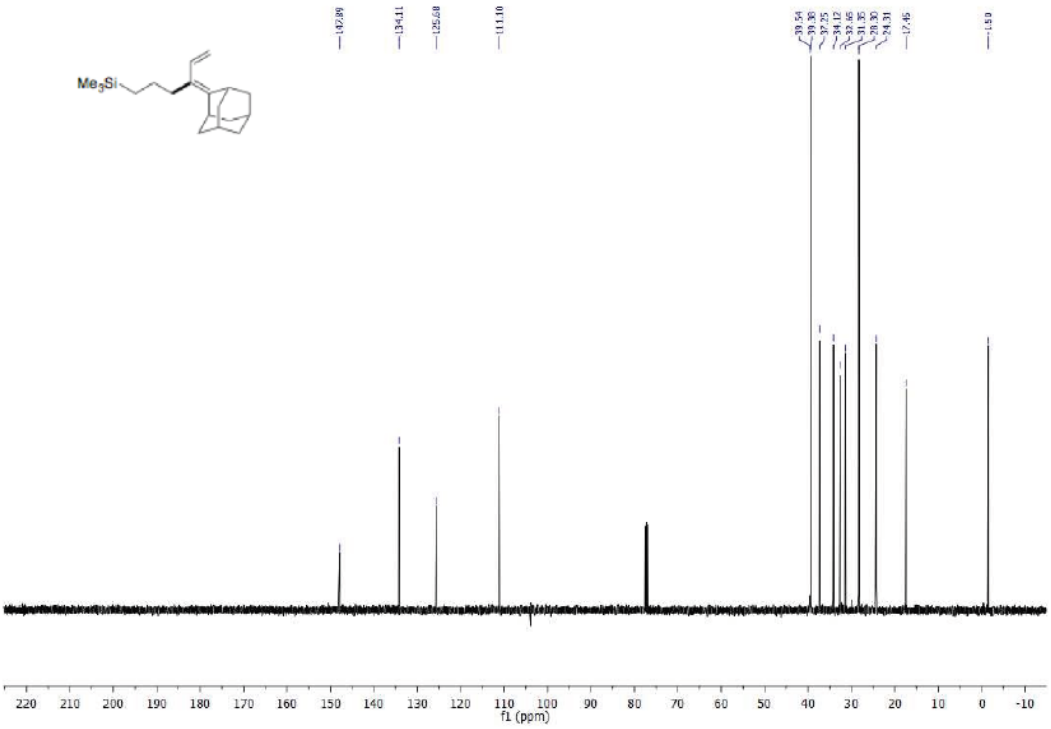

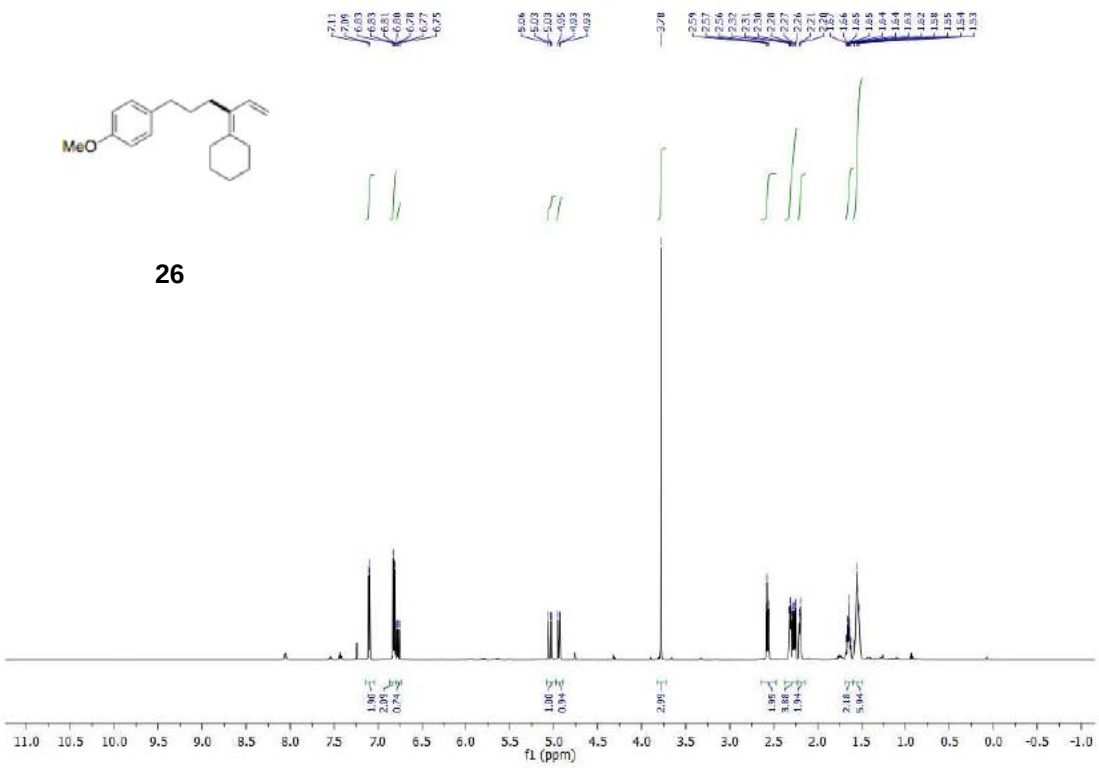

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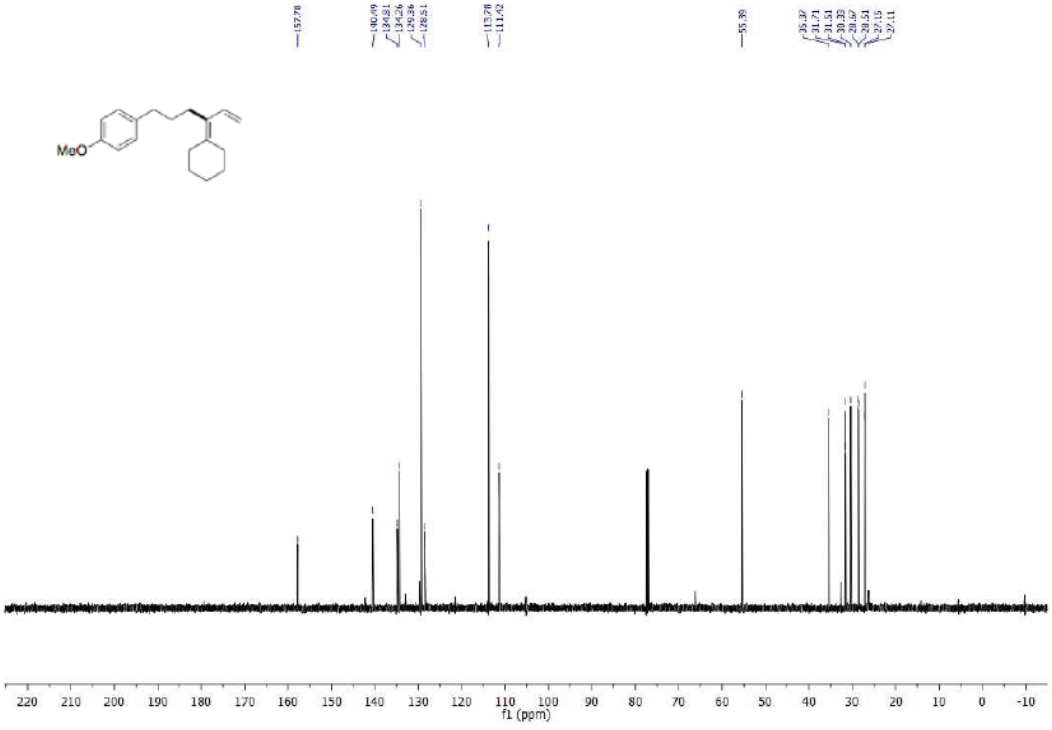

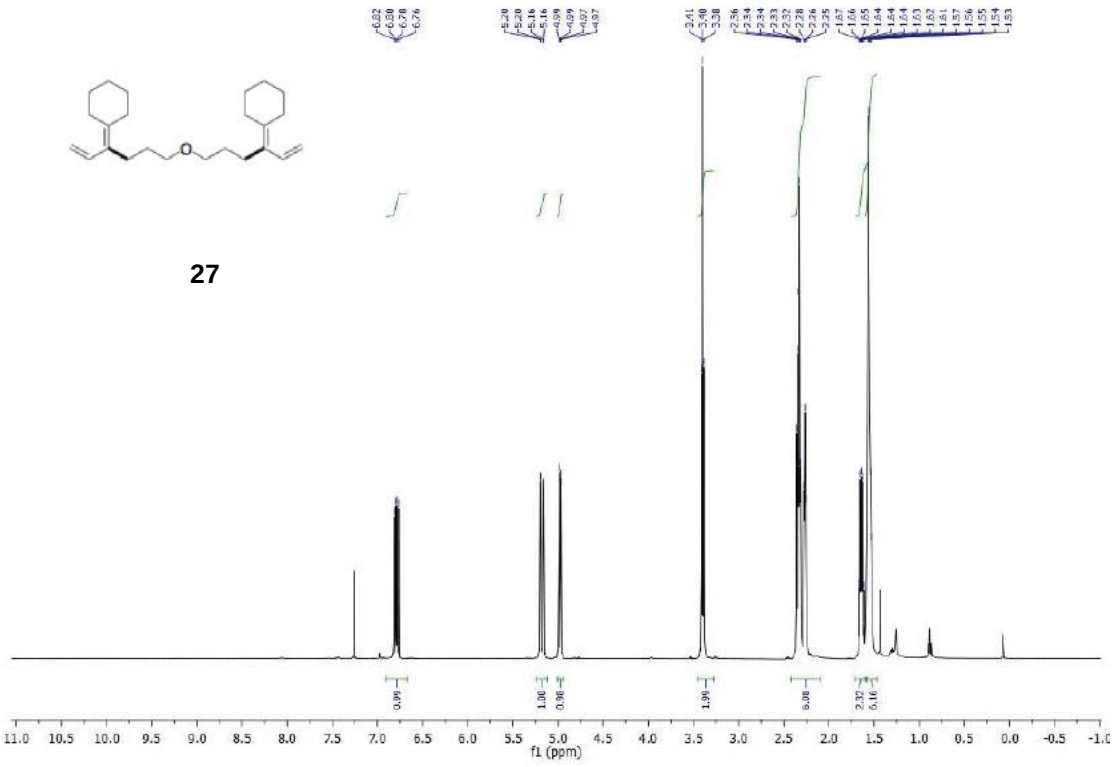

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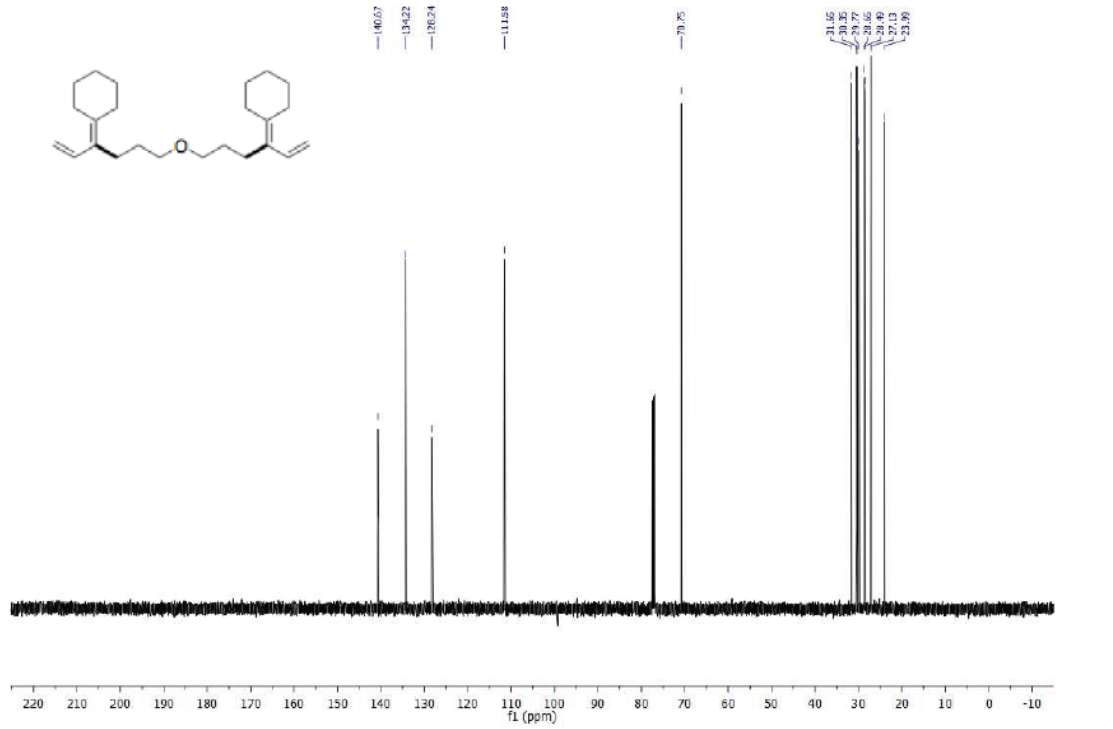

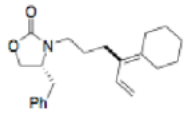

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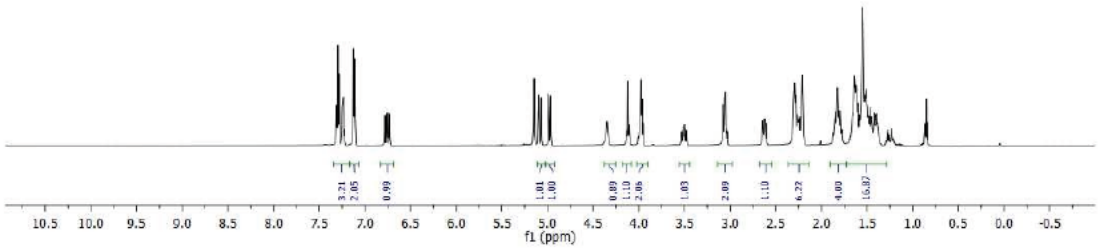
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1.00
0.89
1.10
2.06
1.03
2.09
1.10
6.22
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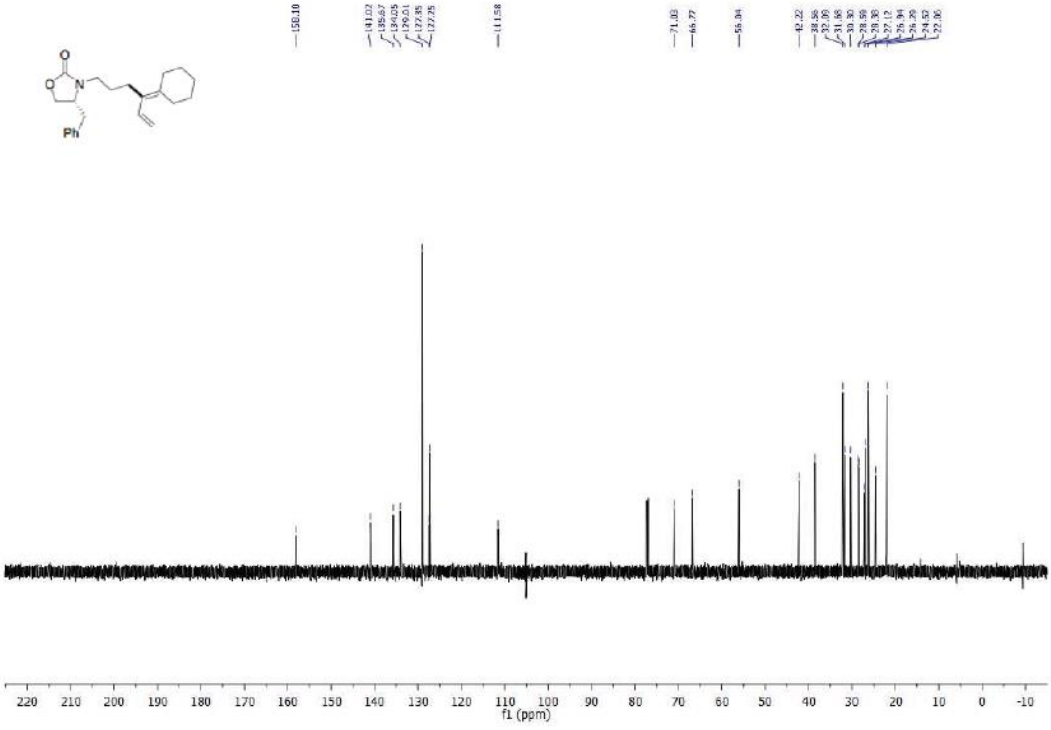
15.87
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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32.96
31.68
30.30
28.99
28.85
27.12
25.94
25.39
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f1 (ppm)

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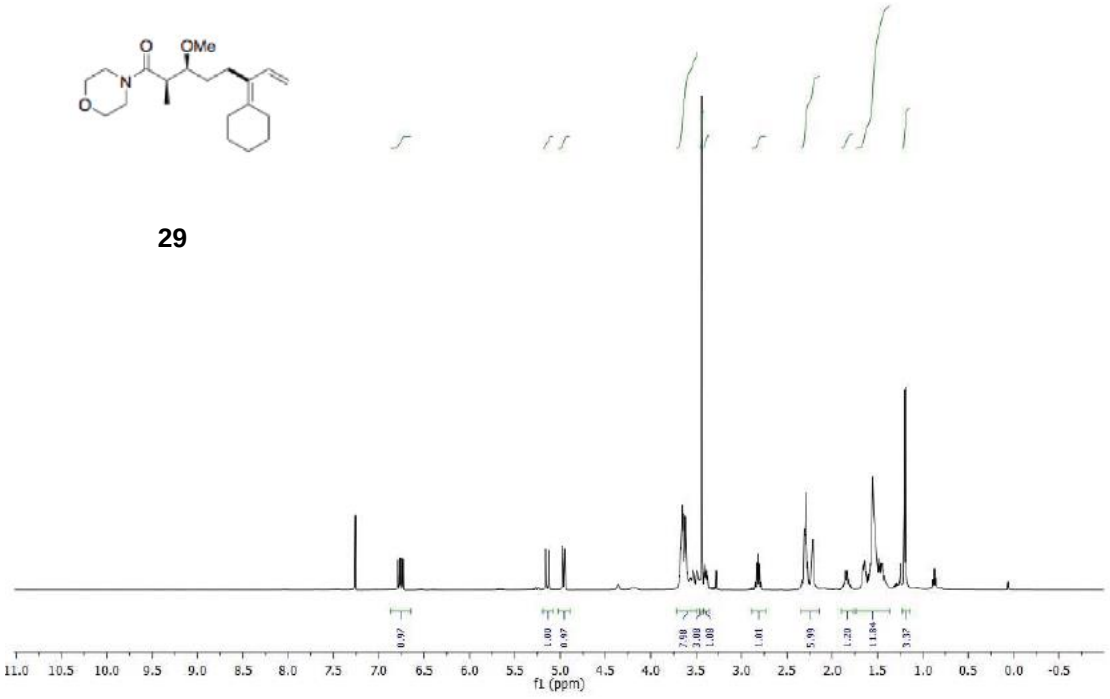
OMe
N
O

29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5.99
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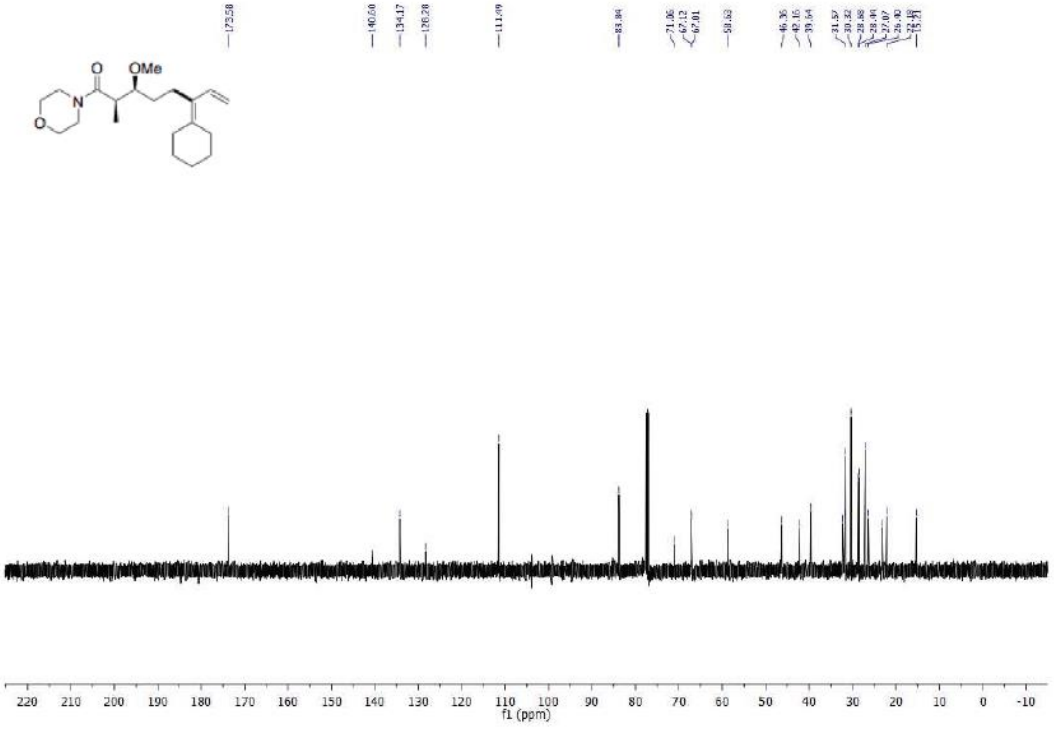
f1 (ppm)

O
OMe
N
O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67.12
67.01
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31.87
29.22
28.98
28.84
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26.90
12.48
15.11
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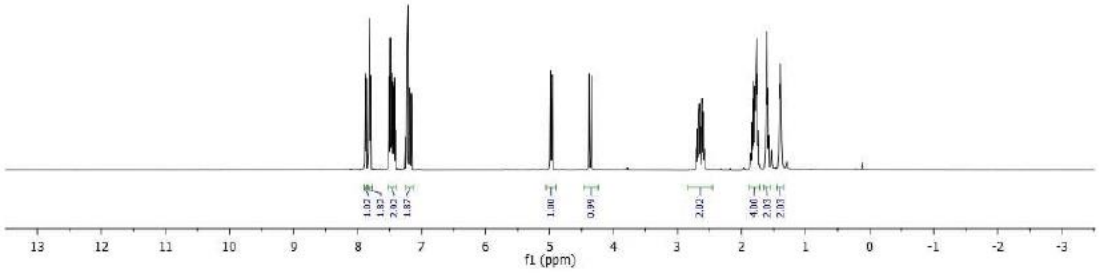
f1 (ppm)

30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1.83
2.02
1.87
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0.99
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4.06
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2.03
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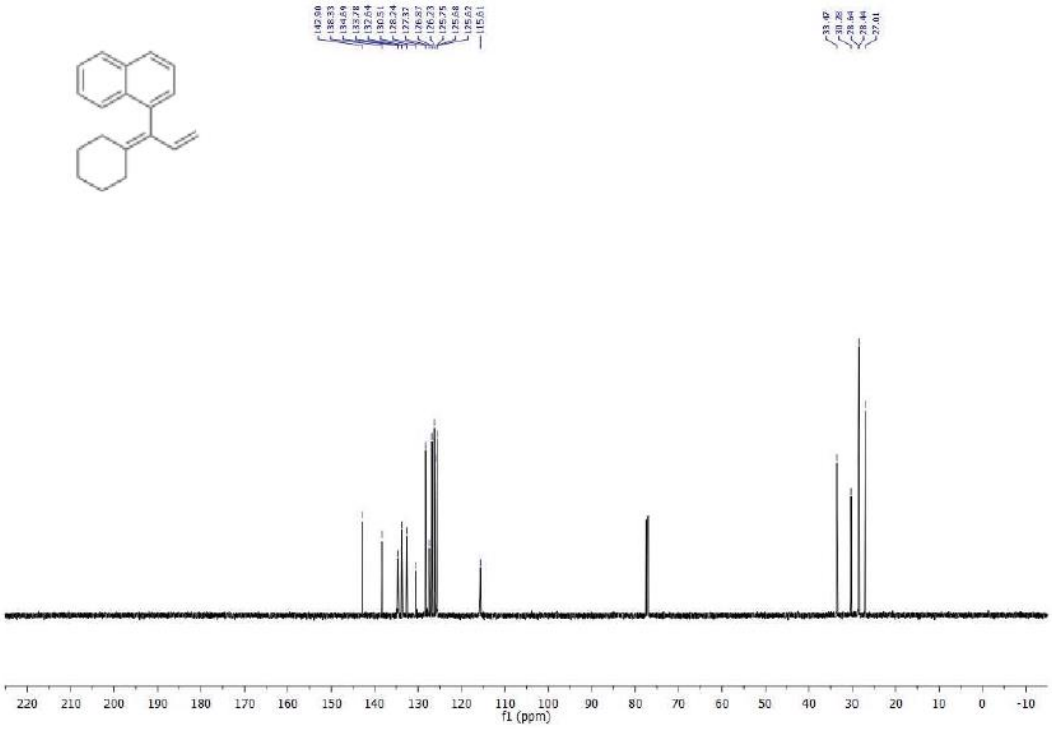
f1 (ppm)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134.46
133.78
132.64
130.51
128.24
127.92
126.87
126.23
125.75
125.56
125.02
115.61
33.47
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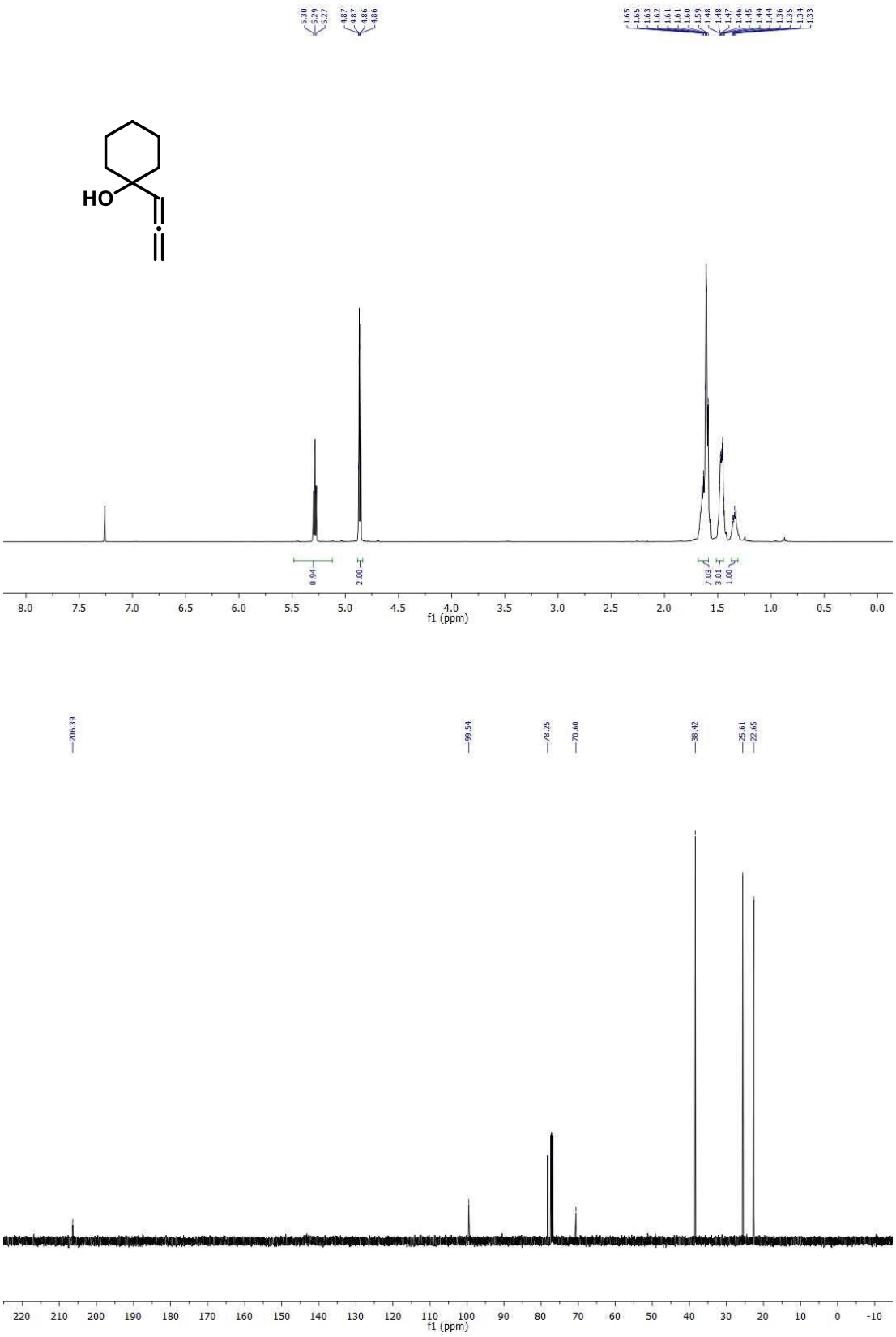
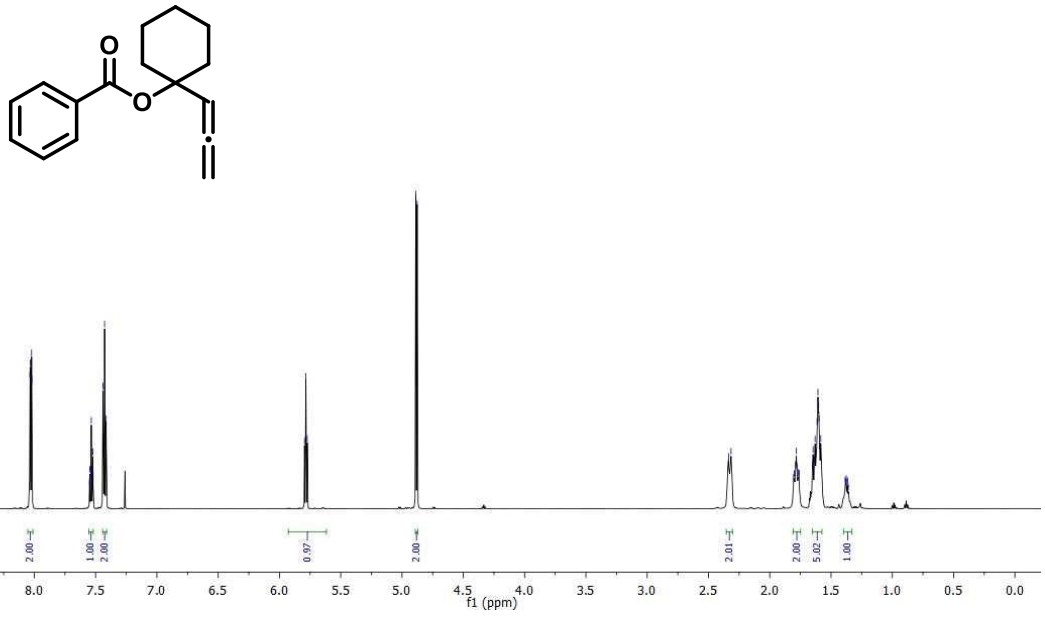
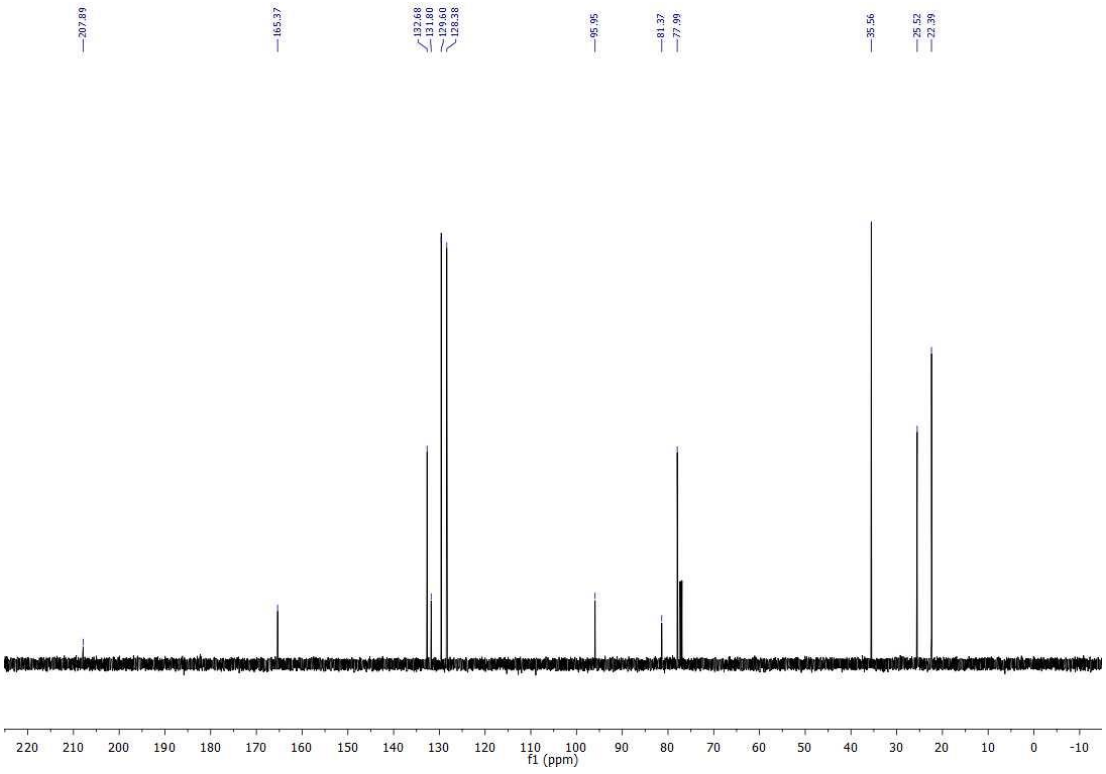
28.64
28.44
27.01
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


HO
f1 (ppm)
f1 (ppm)


O
O
f1 (ppm)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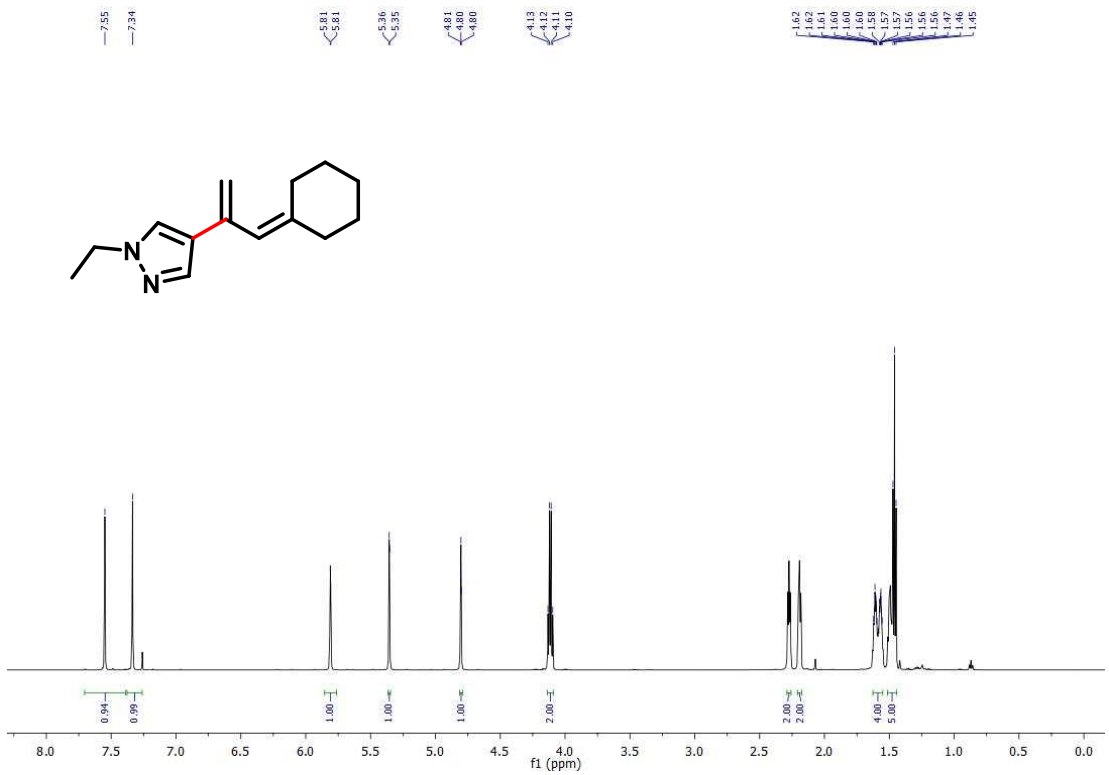
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1.62
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1.61
1.60
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1.58
1.57
1.57
1.57
1.56
1.56
1.56
1.47
1.46
1.45
N
N
0.94
0.99
1.00
1.00
1.00
2.00
2.00
2.00
4.00
5.00
8.0
7.5
7.0
6.5
6.0
5.5
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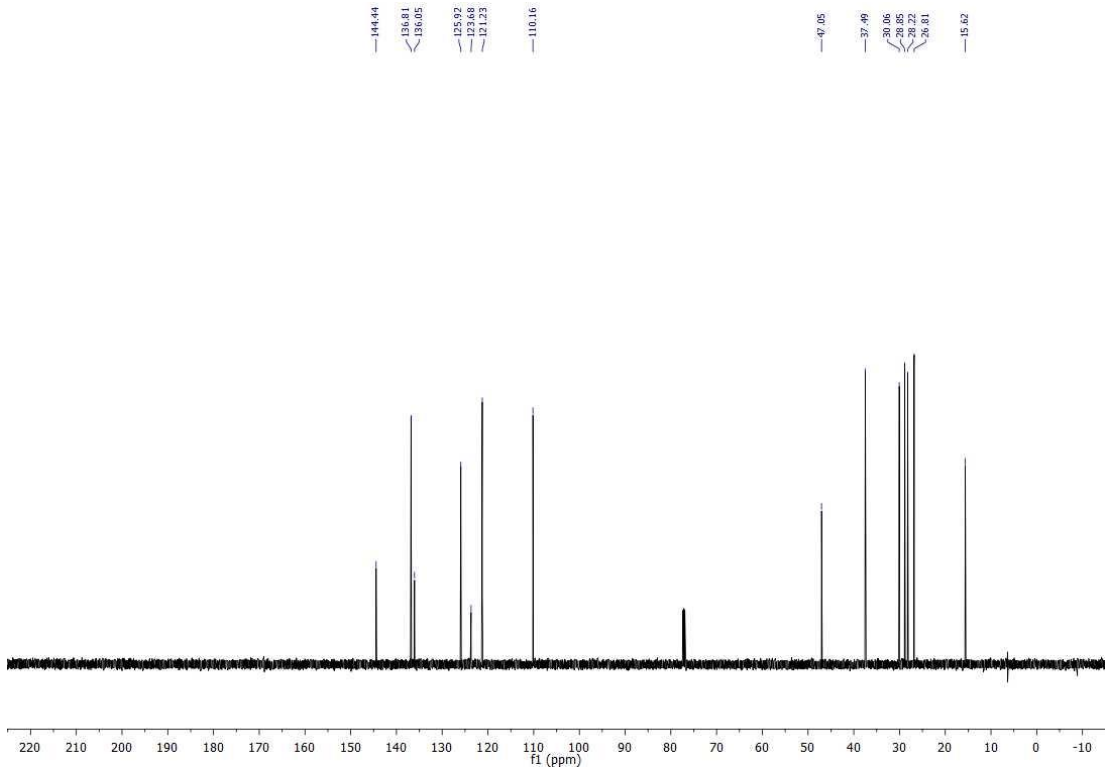
f1 (ppm)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47.05
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15.62
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200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

II. Synthesis of *Functionalized* [3], [4], [5] and [6]Dendralenes through Palladium-Catalyzed Cross-Couplings of Substituted Allenoates

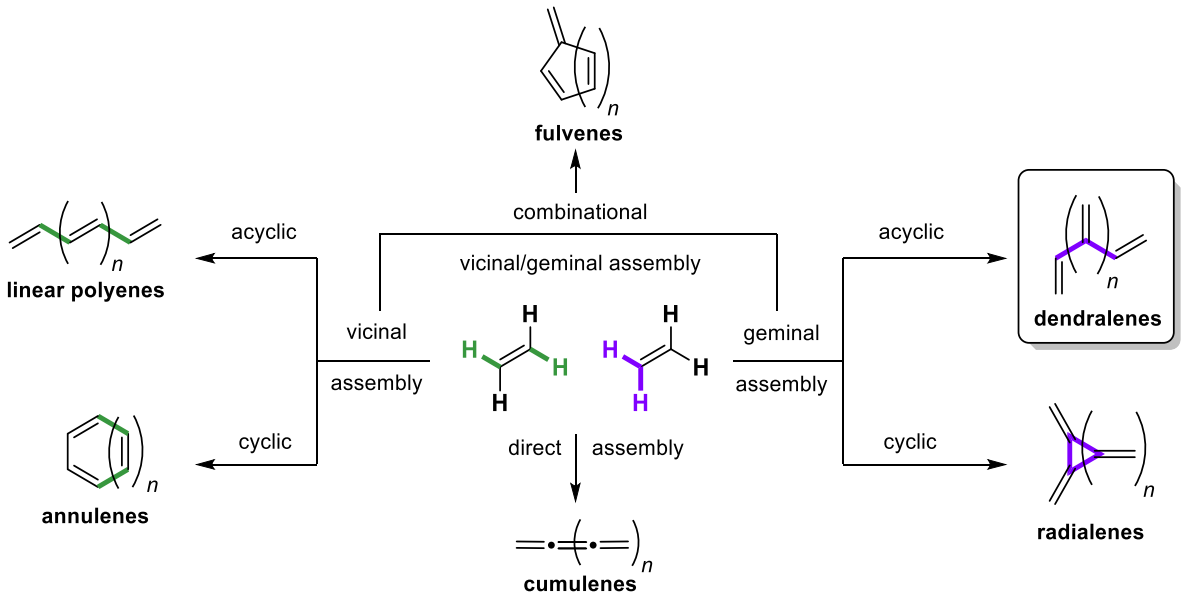
"…so, where are we at with that…'polyene' project ?"

-inquisitively uncertain P.I. in the hallway

2.1. Introduction and Background

Carbon and hydrogen atoms are ubiquitous in all realms of chemistry. More specifically, these atoms, with the aid of oxygen and perhaps nitrogen, form the basis of all material things and Life itself. The thorough studies of the platonic, or parent, systems of hydrocarbon classes have provided scientists with molecular 'rules,' that have aided in guiding scientists rationally through difficult circumstances; thus, forming the basis of reactivity in organic chemistry. Therefore, understanding, or uncovering, these 'rules' is central, and indispensable, to the organic chemist. Of the many sub-classes of hydrocarbons, the family comprised specifically of 'ethylene units' (consecutively connected double bonds) will form the basis of the discussion presented herein.[1]

Figure 1. Classes of Fundamental Hydrocarbons Assembled through Connection of 'Ethylene Units'



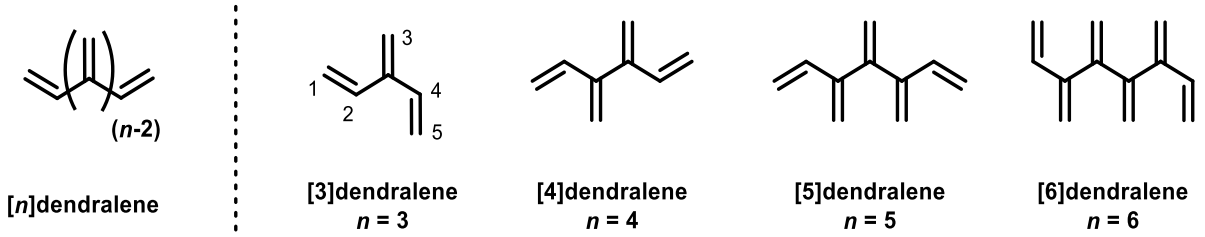
If one takes ethylene, the smallest unsaturated two sp^2-carbon unit, and were to iteratively connect it, in the same fashion with more units, six distinct sub-classes of the 'ethylene family' arise (Figure 1). Connectivity in these cases can be vicinal or geminal, linear or cyclic, combinational (fulvenes), or direct (cumulenes) forms. Of these six sub-classes vicinal assembly produces, by far, the two most abundant, and commonly encountered, motifs in Nature; the linear polyenes (acyclic, vicinal) and the annulenes (cyclic, vicinal). The linear polyenes, starting from the simplest 1,3-butadiene have been 'time-honored' synthetic handles for complexity building; and when conjugation is further extended these polyenes exhibit strong electron conductivity properties; of interest in light harvesting for plant-based life, and materials chemistry devices such as organo-photovoltaics. Furthermore; when cyclic, the

annulenes arise; with the trimer of this sub-class being the universally recognized benzene ring. The annulenes are of particular note as, up until recently, they were the only class of fundamental hydrocarbon to exhibit alternating behavior between the 'odd' and 'even' members, displaying the properties of either 'aromatic' or 'anti-aromatic,' when applying Hückel's $4n + 2$ rule; respectively.[2] Within the annulenes the only other distinctive physical, or chemical, property is the observed alternation in melting points; between even and odd sized rings, a property that was traced back to their level of capacity for molecular packing; *i.e.* the nature of their resulting crystalline lattice's.[3]

In sharp contrast, the products generated *via* geminal assembly produce the more exotic, and significantly less-studied, radialenes (cyclic, geminal) and the dendralenes (acyclic, geminal); the latter of which being the focus of this chapter. While the radialenes have gained increased development throughout the last half a century in both curiosity and utility driven research, the acyclic dendralenes have only recently made their way onto the scene; and much is still to be explored and leveraged for their use.

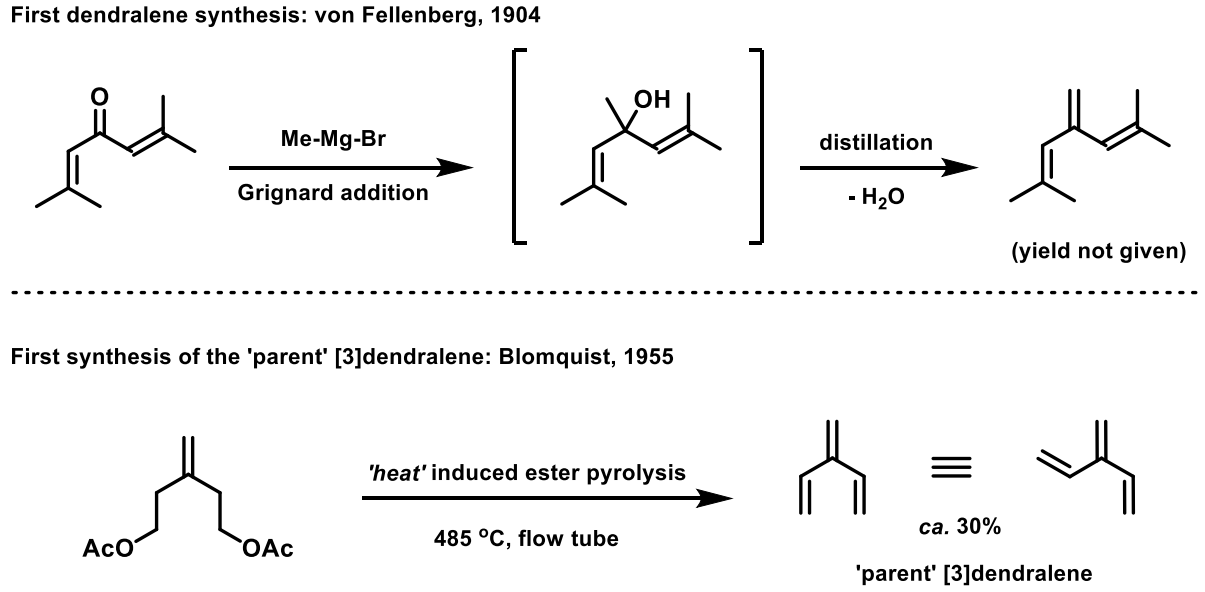
Nomenclature-wise, since a dendralene is formed *via* geminal connectivity of successive ethylene units, the denotation for an undefined length of units in a dendralenic molecule is [*n*]dendralene. By using the template structure in Figure 2 (far left) and applying the (*n*-2) rule, a clear and simple numbering system for oligomeric naming results. Additionally, since 1,3-butadiene does *not* contain any cross-conjugation, it is therefore *not* a dendralene; however, for qualification and analytical purposes, it is sometimes used as a reference molecule (*e.g.* in UV-Vis spectra correlation).

Figure 2. Systematic Nomenclature & Numbering Rules for [*n*]Dendralenes



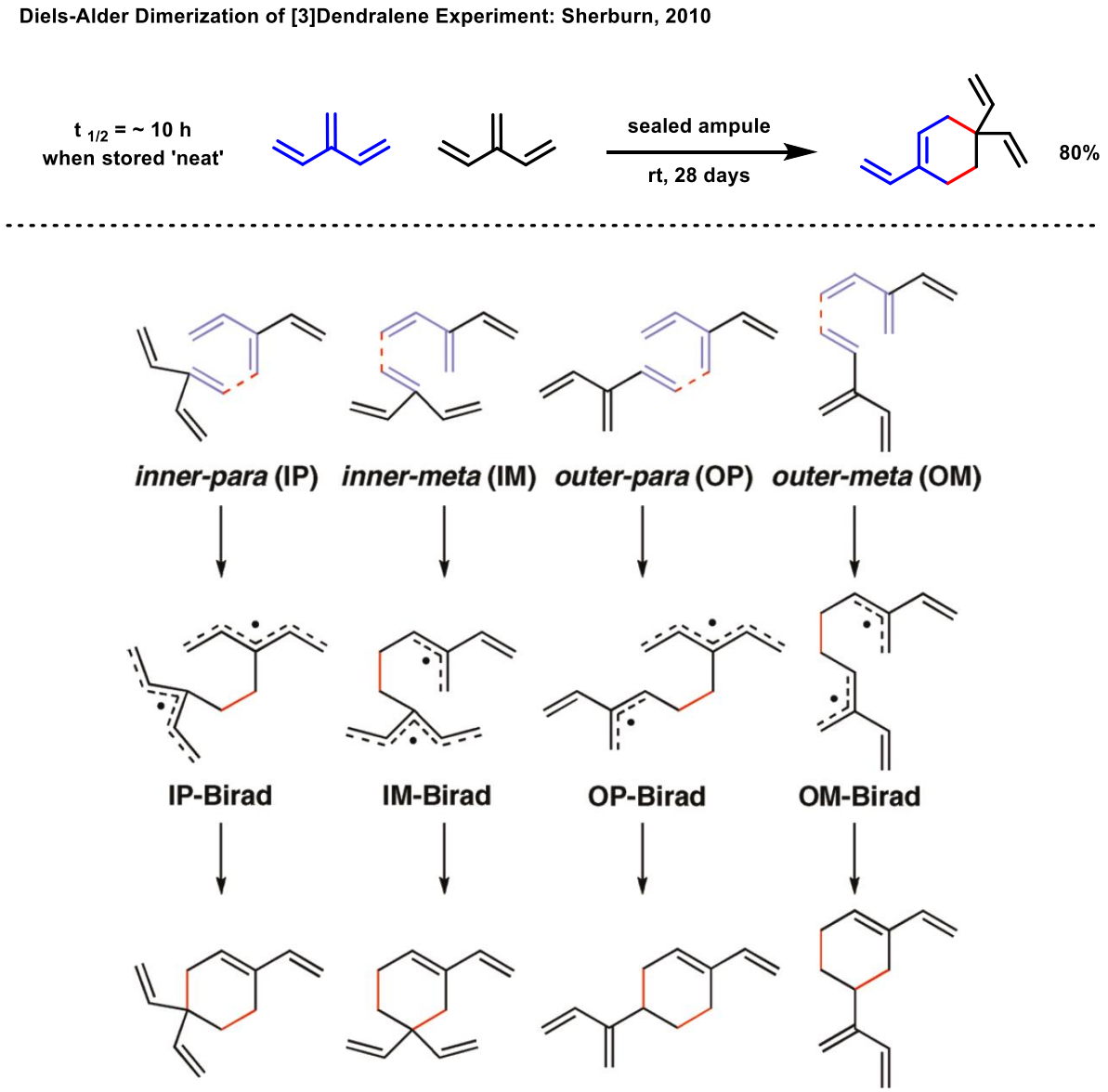
So why was it that this *fundamental* class of hydrocarbon had been *"neglected"* for so many years, especially since the first derivative was prepared by von Fellenberg back in 1904?[4] Note, however, that this was a polymethyl-substituted derivative, and for good reason (Figure 3, top). Moreover; it took over fifty years, after the above-mentioned initial achievement, for the 'parent' [3]dendralene to succumb to synthetic efforts (Figure 3, bottom).[5]

Figure 3. First Reported Syntheses of a Dendralene



The reason for this large gap in time (*i.e.* 1904 - 1955), and the equivalently large gap since (*i.e.* 1955 - 2000) is simple, yet, border-line disappointing. The unsubstituted versions of these molecules (*i.e.* parent molecules) were placed in a credendum of which one could not isolate the pure material in useful quantities, without engaging in their inevitable decomposition pathways (*e.g.* [4 + 2] Diels-Alder dimerization/polymerization) (Figure 4).[6] How unfortunate this was! Starting in the year 2000, now 18 years later, these molecules are progressively gaining attention and applicability in both methodology developments and natural products synthesis; with regard to both their construction and utility in synthesis. At times it becomes compelling to imagine what the progression in this particular field would be today, if this dogma was questioned decades ago…similar to the 'acceptance/breakthrough' the cumulenes, namely allenes, have had since their rapid "boom" around the 1990's.[1a,7]

Figure 4. Diels-Alder-Dimerization Analysis[6]



Now, to be fair, analysis of hydrocarbon materials and their decomposition products during these early years were less than trivial; where the usual technique was to globally reduce all un-saturations to the corresponding hydrocarbon, of which one hopefully had an authentic sample of for boiling point, melting point, IR and UV-Vis comparisons (NMR analysis eventually being developed between the late 1940's and early 1950's).[8]

This ‘dimerization’ product was determined to be that shown in Figure 4 (top); due to the ability for, namely, [3]dendralene to rest in a ‘biradicaloid’ state. Of the four possible transition-states for this unusual Diels-Alder (D.A.) dimerization (Figure 4, bottom) the ‘inner-para’ (IP) transition-state is vastly predominant; this is likely due to the presence of two delocalized penta-dienyl radical species within such a transition-state of the newly developing C-C bonds. In contrast, the other three feasible transition-states contain at least one less stable radical species; in the form of an allyl radical (IM, OP, and OM).

This stability issue (inherent D.A. dimerization) could be reconciled by either isolating and storing the material as dilute solutions in THF, or by storing properly designed precursor molecules and simply liberating the dendralene moiety within a few hours of use. The realization of the later discovery of ‘masking,’ simple as it may appear, was crucial for ‘*de-mystifying’* this class of molecule, allowing for the flood-gates to open; at least for one research group. It would be the group of Prof. Mick Sherburn (Australian National University) to take the lead and embark on a synthetic mission to truly understand the chemical and physical properties of dendralenes. This was achieved through successive, often ingenious, improvements on previously developed routes to construct ‘useful quantities’ of the parent [*n*]dendralenes (unsubstituted compounds). The initial synthetic “break-through” (as it was described by Hopf)[9] implemented ‘rock-solid’ vinyl-sulfolene derivatives, which formally served as ‘masked’ [*n*]dendralenes. Upon heat-induced cheletropic elimination, *via* a Ramberg-Bäcklund pericyclic process, extrusion of sulfur dioxide liberated the desired [*n*]dendralene in milligram quantities; more than enough for first generation analytical analyses.[10] Although of less, direct, synthetic value at the bench *per se*, these parent syntheses

were necessary to persuade the chemical community of the overall potential utility and value of dendralenes.

Fifteen years after this "break-through" (2000 – 2015) a large series of parent molecules were eventually successfully synthesized, ranging from [3]-[12]dendralene; with the [5]-[12]dendralenes being prepared for the first time *ever* in the literature. Through a combination of physical (**A**), experimental (**B**), and theoretical (**C**) analyses of the first six members of the acyclic, geminally connected, cross conjugated polyethylenes ([3]-[8]dendralene), the first observation of alternation in chemical behavior since that of the annulenes (*vide supra*) by Hückel in 1931[2] was observed, in 2009, by the Sherburn research group.[11] It wasn't until seven years after this achievement (2016) that the 'higher' members of the family, namely [9]-[12]dendralene, were synthesized and also subjected to equivalent analyses (**A** – **C**), as were the lower members. It was with these increasingly larger oligomers that a novel phenomenon was unveiled. By combining the data sets of all [3]-[12]dendralenes it was observed for the first time, with respect to *any* known class of fundamental hydrocarbon or *any* series of related structures, that the dendralene family exhibits a *diminishing alteration* in chemical behavior.[12]

Key findings in the 'parity-dependent' alternation in behavior of the [*n*]dendralenes were manifested throughout the following forms of analysis:

(A) Physical/ Spectroscopic Analysis:

The first major discrepancy noticed between the *even* and *odd* family members was their relative stability upon isolation and storage. This was the Achilles' heel, so to speak, of initial efforts, as the smallest member (also the smallest odd member) [3]dendralene was determined to be the *least* stable of *all* dendralenes; conversely the smallest even member, [4]dendralene, was determined to be the *most* stable of *all* dendralenes prepared thus far. This characteristic feature of stability-instability is inversely related to their chemical reactivity (see sub-section

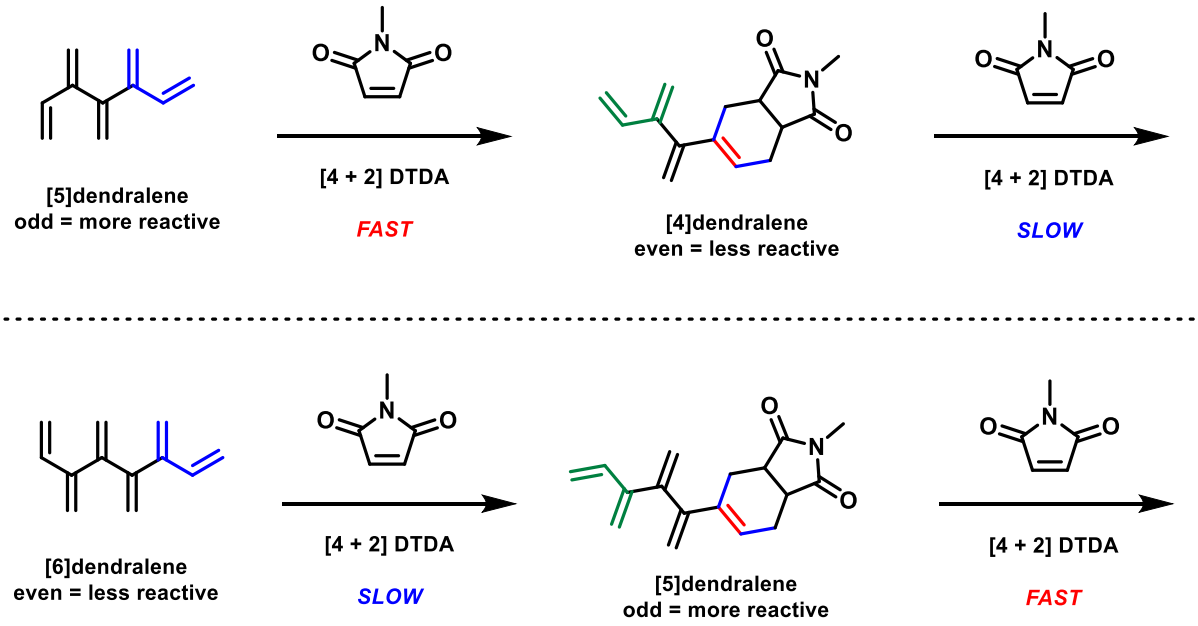
B, below). Although UV-Vis analysis of the (all *E*-) linear polyenes shows gradually increasing wavelengths (λ_{max} *ca.* 25 nm) for each additional conjugated olefin, the family of [*n*]dendralenes exhibit a single UV-Visible maximum absorbance at λ_{max} 215-216 nm (in hexane). This value of which is strikingly similar to that of 1,3-butadiene (λ_{max} = 217 nm), is suggestive of their inherent nature to act as, or adopt in resting-structure, poly-1,3-butadiene moieties (of orthogonal 90^{o} inter-connection); with the exception of [3]dendralene which shows two maxima absorptions at 206 and 231 nm.[1b,1c,11,12] Yet, with increasing oligomeric members, a relatively equal increase in the molar extinction coefficient is observed throughout. By taking these molar extinctions and plotting their values against the number of C=C units within the structure an impressive pattern is revealed. Opposed to incremental progression with each additional ethylene unit, an 'up-down' pattern is observed; in which the magnitude of difference decreases as chain length increases. Furthermore; simple NMR studies, of over-lay spectra, for both proton and carbon nuclei, show an obvious 'zig-zag' pattern which likewise, with increasing C=C units, progressively centralizes to a point of equality (again with [3]dendralene being an unusual outlier).

(B) Experimental/ Reactivity Analysis:

As noted above, stability and reactivity are inversely related. Thus, the odd-dendralenes (less stable) are exceedingly more reactive than the even-dendralenes (more stable). This was studied, experimentally, with regard to their proclivity to engage as educts in the Diene-Transmissive-Diels-Alder [4 + 2] cyclo-addition reaction (DTDA); where yet again, parity dependence excelled at first and then slowly became unified at extended [*n*]-family lengths. Each of the ten representative [*n*]dendralenes were subjected to exposure to one equivalent of the dienophile *N*-methylmaleimide (NMM), dissolved in deuterated chloroform at room-temperature in a sealed NMR-tube. Reactions were monitored until full consumption of the

dienophile was observed, at which point the contents of the reaction mixtures were subjected to column chromatography, on silica gel, to assess the ratio of unreacted starting material : mono-cycloaddition : bis-cycloaddition reaction components. Both mono- and bis- adducts predominately took place at the terminal diene sites, the exception being that of [4]dendralene which preferentially undergoes its first cycloaddition at the internal diene site (see sub-section **C**, below).

Figure 5. Parity-Dependence Driven DTDA Reaction Rate and Selectivity



For the odd members ([3], [5], [7], [9] and [11]dendralenes) the major product upon isolation reflected predominately mono-addition adducts of terminal diene regioselectivity; accompanied with slow but gradually increasing populations of the bis-adducts. The preference for mono-addition is to be expected for odd members since the product, after the initial cycloaddition, is now an *even* dendralene (which are collectively less reactive; Figure 5). The preference for regioselectivity about the terminal diene-site is due to conformational

preference (see sub-section **C**, below). On the other hand, for even members ([4], [6], [8], [10] and [12]dendralenes) no distinguishable selectivity for mono-cycloaddition is observed. Instead, mixtures of mono- and bis-cycloaddition adducts, along with unreacted starting [*even*]dendralenes were observed throughout the even-membered set; which gradually begin to produce more mono-adducts, as well as less starting material and bis-adducts, with ascension of the even-membered-family. Thus; when an even (less reactive) dendralene undergoes cycloaddition *via* the DTDA sequence, the resulting transmitted diene moiety now contains an *odd* (more reactive) dendralene. This even-to-odd-to-even-to-odd pattern is therefore assumed to be responsible for the lack of selectivity in the even-membered series, and the high level of selectivity in the odd-membered series.

(C) Theoretical/ Computational/ Conformational Analysis:

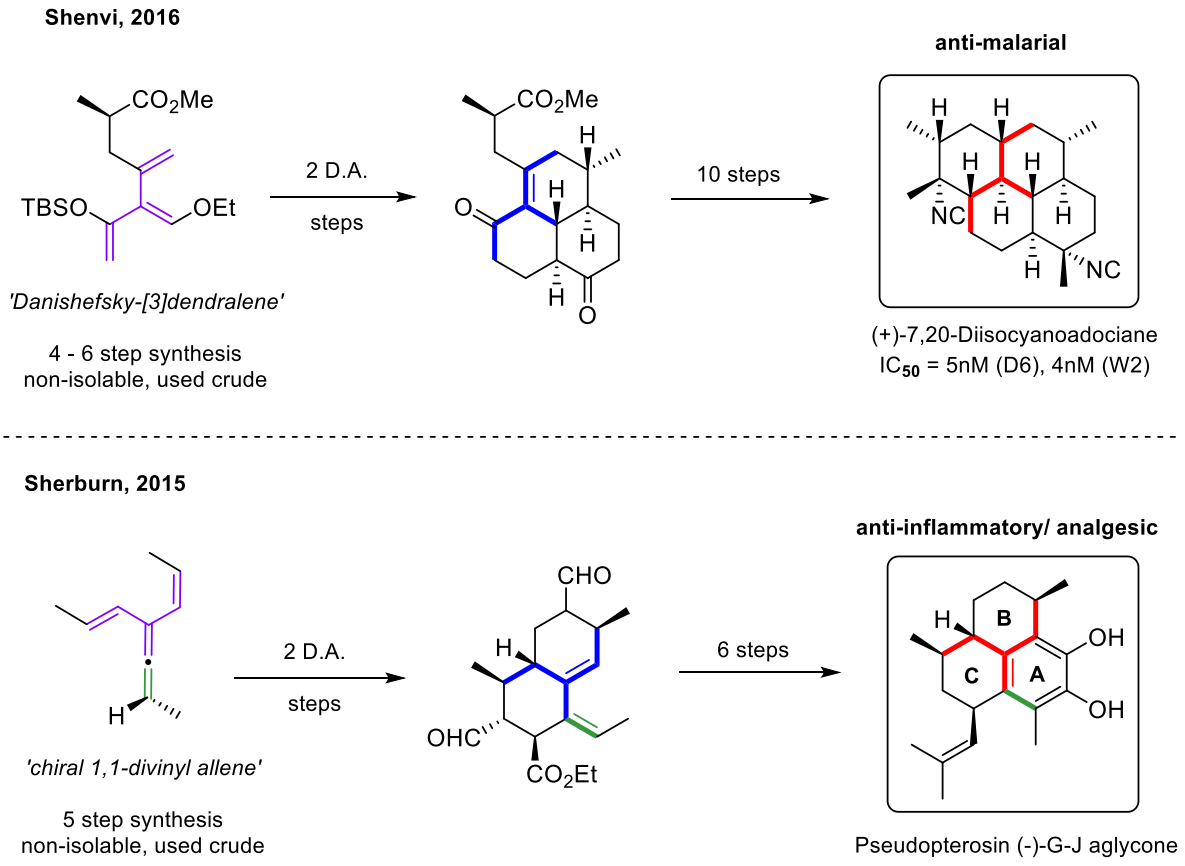
The origin of the stability-reactivity antithesis of the dendralene's even-odd parity was computationally traced back to conformational and energetic barriers, as well as the (ever-increasing) magnitude of possible resting-states of equal, or similar, energies. That is, with increasing values of *n*, for the *n* + 2 equation (*vide supra*), there are exponentially increasing numbers of conformations of the cross-conjugated dendralenic 'back-bone.' In other words, the potential exists to adopt either an *s-cis* or *s-trans* geometry. Coupled with the ability to orient in any of three possible conformations, for any of the given *pseudo*-butadiene residues within such an oligomer (*i.e.* gauche-gauche, anti-gauche, and anti-anti), these increasing populations eventually out-weigh any other molecular characteristic of the dendralenes, leading to their novel *diminishing* alternation in chemical behavior.[1b,1c,11,12]

Therefore, with this advent of new chemical space, many exciting applications utilizing this unique and virtually 'un-tapped' moiety are envisioned to be forthcoming. One of many attractive features, of the dendralenes framework is their ready ability to participate in [4 + 2]

cycloaddition reactions, in particular the DTDA reaction. In this regard, they are exceptionally well configured to maximize "step economy" *en route* to both natural and unnatural materials that contain polycyclic arrays.

Now, no longer simply molecules of curiosity, in large measure due to the Herculean efforts of pioneers such as Prof. Henning Hopf and more recently Prof. Michael S. Sherburn, dendralenes of both the cyclic and acyclic varieties have become useful intermediates in targeted syntheses.[1b,1c,9,13] As demonstrated, by the research group of Prof. Shenvi, the highly potent anti-malarial natural product, (+)-7,20-diisocyanoadociane was synthesized in 17 linear steps (13 steps from simple building blocks) as a single enantiomer. Compared to prior syntheses, of 40 steps (with stereo-control) or 27 steps (effectively providing a racemic mixture of diastereomers), the overall brevity and avoidance of protecting group chemistry makes this an exquisite synthetic route.[14a,14b] Key to the underlying effectiveness, here, was their retro-synthetic analysis of the all-*trans*-fused polycyclic framework, which was referenced back to an electronically-biased, chiral, *'Danishefsky-[3]dendralene'* (Figure 6, top).

Figure 6. Dendralenes as Key Intermediates in Natural Products Total Synthesis[14]



Likewise, in 2015 a remarkably concise synthesis of pseudopterosin (-)-G-J aglycone was achieved in 10 steps (chiral pool) or 11 steps (enantioselective), while the most effective previous efforts were between 14 steps (longest linear sequence, chiral pool) and 20 steps (longest linear, enantioselective).[14c] Key to this achievement was employment of an intriguing chiral, 1,1-divinyl allene, as a highly π-bond-rich carbon scaffold, which quickly furnished the desired fused-decalin scaffold in only two steps (Figure 6, bottom) and with properly set chirality! An initial Diels-Alder cycloaddition afforded an intermediate which, due to transmission of the diene moiety, resulted in a *semi*-cyclic [3]dendralene. This intermediate is equally well suited to participate further in a, yet again, subsequent Diels-Alder reaction,

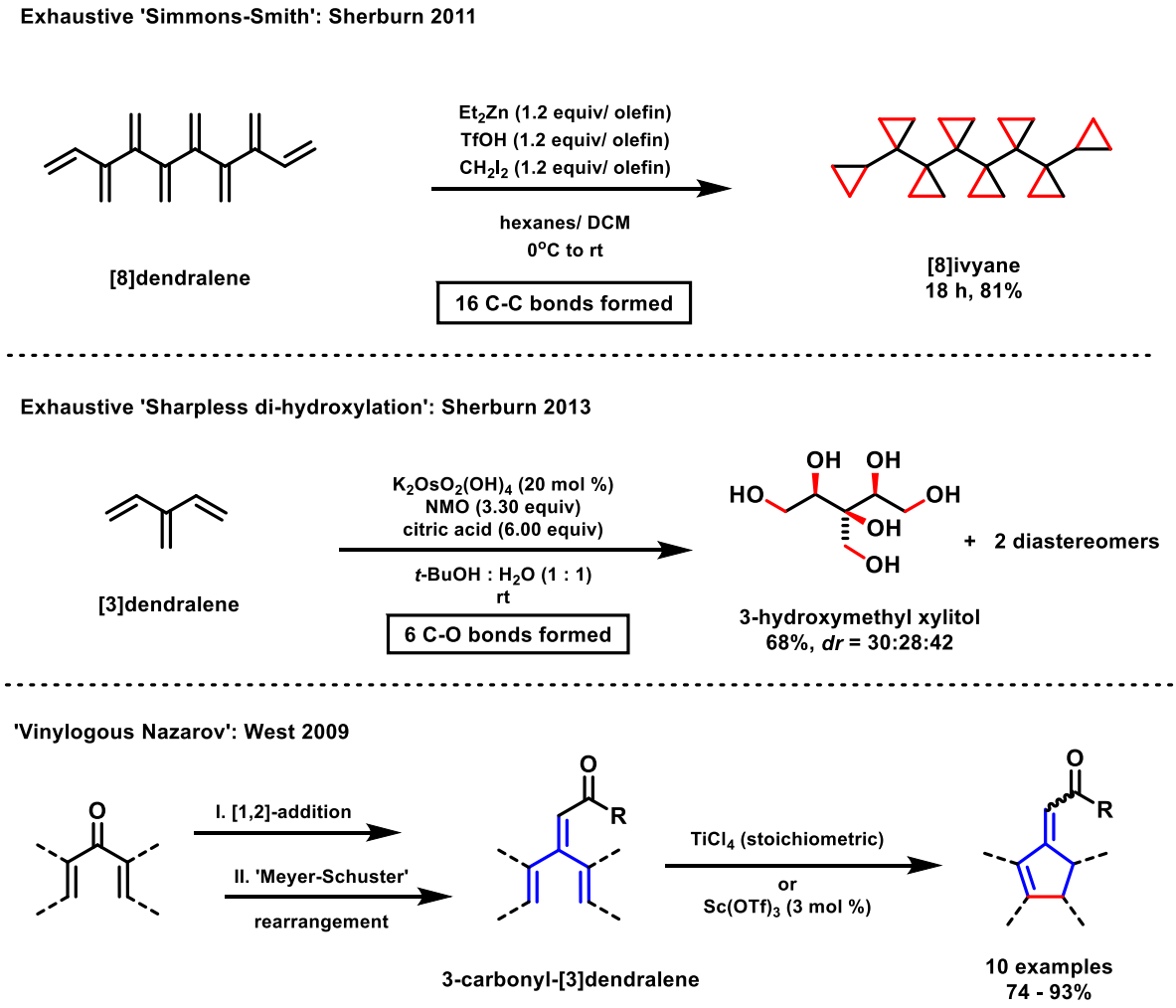
ultimately arriving at both the 'B' and 'C'-rings of the natural product with the central-core being composed of those carbon atoms initially in the form of the starting (centrally-cumulated-[3]dendralene) 1,1-divinyl allene. Of note in this approach is that with this 'cumulated-[3]dendralene (odd), after the initial D.A., diene transmission furnishes another [3]dendralene; the only instance I'm aware of where and odd dendralene produces another odd dendralene upon DTDA cycloaddition.

Notwithstanding the remarkable advances made in preparing higher homologs that now have reached [12]dendralene,[12] recent papers from the Sherburn group (which is effectively the world-authority on dendralene chemistry) highlight the need for additional inroads to both the parent and especially substituted systems; as well as new chemistry that extends the repertoire of reactions of dendralenes beyond [4 + 2] cycloadditions. Indeed, in a recent Account,[15] Sherburn concludes: *"Regarding our deployment of the dendralenes and related unsaturated hydrocarbons in the rapid generation of structural complexity, again, we have deployed only known reactions (and in the main, just one: the venerable Diels-Alder reaction)."*

Other than the Diels-Alder reaction, there are less than a handful of other reactions in the literature which engage dendralenes, demonstrating further functionalization, other than isolated examples of otherwise un-related research. As shown in Figure 7 the most common technique for dendralene derivatization is that of exhaustion; in the forms of either a global 'Simmons-Smith' (top) or a global 'Sharpless dihydroxylation' reaction (middle). These approaches delivered both the [*n*]ivyanes and the sugar natural product 3-(hydroxymethyl)xylitol; respectively. The latter case resulted in the re-assignment of the originally proposed structure.[16b] The former case sparked the interest of NASA's jet

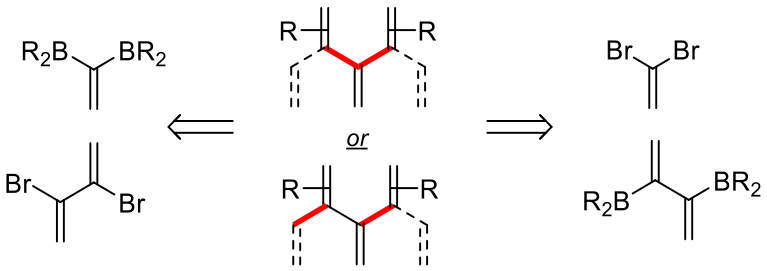
propulsion laboratory; due to their abnormally high enthalpy of combustion as a function of weight; exceeding even that of cubane.[16a] The third, and only other, example to date (as far as the author is aware of) comes from an elegant 'vinylogous Nazarov' reaction by the West group (Figure 7, bottom). The success of this study necessitated the development of a methodology to first access the precursor 'trienoates,' or 3-carbonyl-[3]dendralenes.[16c] Preparation of these Nazarov educts centered around a two-step sequence in which 1,2-addition of a lithiated ethyl ethynyl ether, followed by 'Meyer-Schuster' rearrangement catalyzed by $VO(acac)_2$, afforded the desired highly polarized [3]dendralenes; readily poised for electro-cyclization.

Figure 7. Few Known Reactions of Dendralenes in Literature, Other than the DTDA[16]



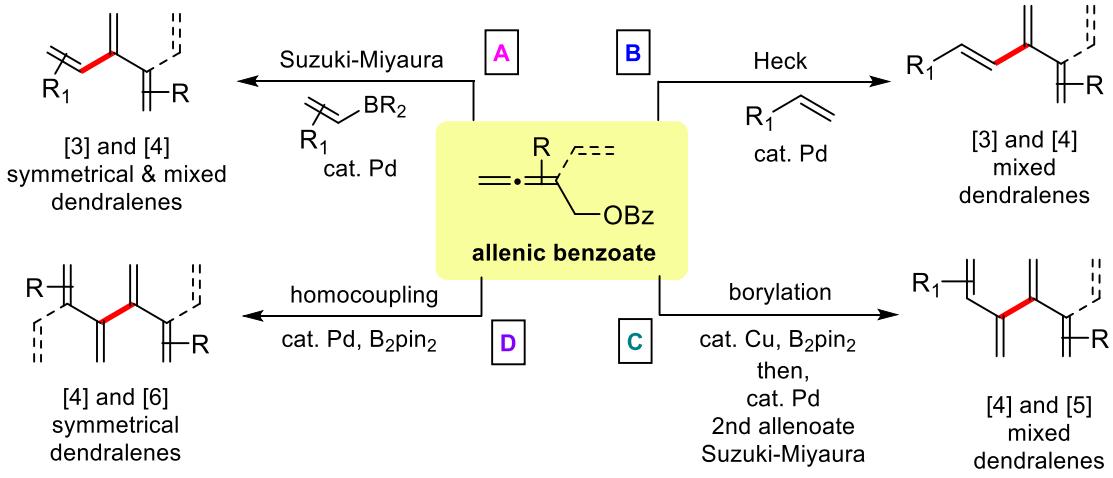
Other reactions of functionalized dendralenes, especially those associated with higher homologs that are regioselective, are few in number.[1c,15] Since most published routes to dendralenes involve double cross-couplings from dihalo- and diborylated intermediates (Figure 8)[10,11,12,17] selective mono-functionalized and unsymmetrical patterns, which are likely to prove more valuable in total synthesis, remain few in number.

Figure 8. Common Disconnections to Access Dendralenes; (prior art)



We, therefore set out to develop a methodology that provides solutions to these shortcomings. The research that follows provides rapid access to both functionalized symmetrical and unsymmetrical [3]–[6]dendralenes from a common allenic precursor, using palladium-catalyzed cross-couplings under micellar catalysis conditions; *i.e.*, in water and typically at ambient temperature (Figure 9).[18] Additionally, regioselective manipulations such as epoxidations, conjugate additions and olefin metathesis reactions, the *first* of their kind among dendralenes and their derivatives, are also illustrated.

Figure 9. General Synthetic Routes, A–D, Utilized to Prepare Dendralenes; (this work)



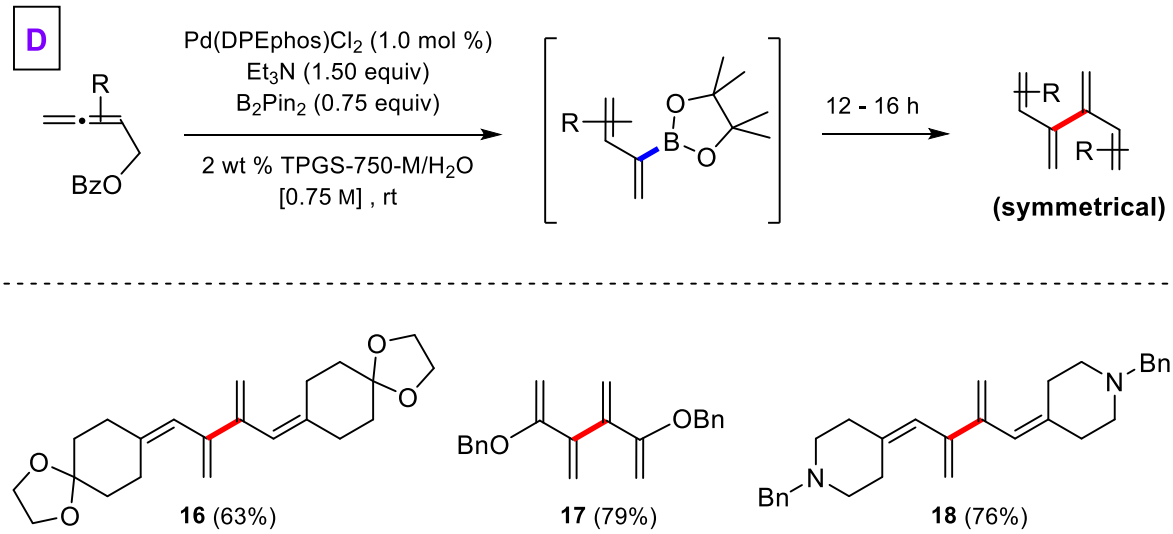
2.2. Results and Discussion

While further pursuing the potential of allenic esters to act as competent, electrophilic, 1,3-butadiene precursors (see Chapter I), initial attempts to effect a 'net' Miyaura-borylation were, at the time, met with frustrating results. Under numerous palladium-catalyzed conditions, when the starting allenic ester was mixed in the presence of B_2Pin_2 and base (Et_3N), only low amounts of the desired 2-borylated-1,3-butadiene were isolated; with the major product being the result of an undesired side-reaction. Upon time-point analysis of a control reaction, it was observed that a statistical mixture of three entities persisted throughout extended reaction times. These components were identified as: starting allenic ester, desired borylated butadiene, as well as a third off-cycle "*homocoupling"* by-product; which at ~50% conversion provided a ratio of roughly 2 : 1 : 1, *via* gas-chromatography mass-spectrometry (GC/MS) analysis. The latter component reflects an initial Miyaura-borylation to afford the originally

sought after borylated-diene, that once produced is an equally competent nucleophilic coupling partner (as compared with B_2Pin_2) which competitively re-enters the catalytic cycle and engages in cross-coupling. Thus, a combinatorial, dual-catalytic mechanism was in operation here, relaying the products/intermediates of a Miyaura-borylation cycle into that of a Suzuki-Miyaura; hence the observed, curious, product-distributions of the reaction mixture at half conversion. Ultimately, this 'by-product' was a symmetrical [4]dendralene. I had not yet known of this type of molecule…and neither did *almost* anyone else (even if you can read Russian). Nevertheless, apparently, we could make them; and pretty easily too. This was my first account of synthesizing and shortly later being made aware of what a '*dendralene'* is/ was/ and can be (see section 2.1).

In retrospect, however, this was somewhat to be expected. Traditionally, realization of the Miyaura-borylation is inherently reliant upon the base employed. That is, due to the close similarity to that of the Suzuki-Miyaura cross-coupling mechanism (which takes advantage of the electrophilicity of an organo-boron species towards base-mediated activation) the nature, and more specifically the pKa, of the base is absolutely crucial. To this end, the most commonly utilized base for the Miyaura-borylation is either the sodium or potassium salt of the acetate anion (pKa ~ 4.76 in water, ~ 12.3 in DMSO);[19] which is strong enough to activate the di-boron reagent for nucleophilic participation, *via* transmetallation, yet is weak enough of a base as to *not* activate the borylated product for subsequent cross-coupling. In contrast, the Suzuki-Miyaura mechanism requires a, relatively, stronger base for its success. Commonly employed bases, here, being hydroxide, potassium phosphate, carbonates and triethylamine (Et_3N); the latter of which was likely the culprit component that allowed for this serendipitous discovery of *'homocoupling;'* a pathway first observed by Welker over a decade ago.[17g]

Scheme 1. B_2Pin_2/ Suzuki-Miyaura-Mediated 'Homocoupling' for the Synthesis of Symmetrical [4]Dendralenes (D)



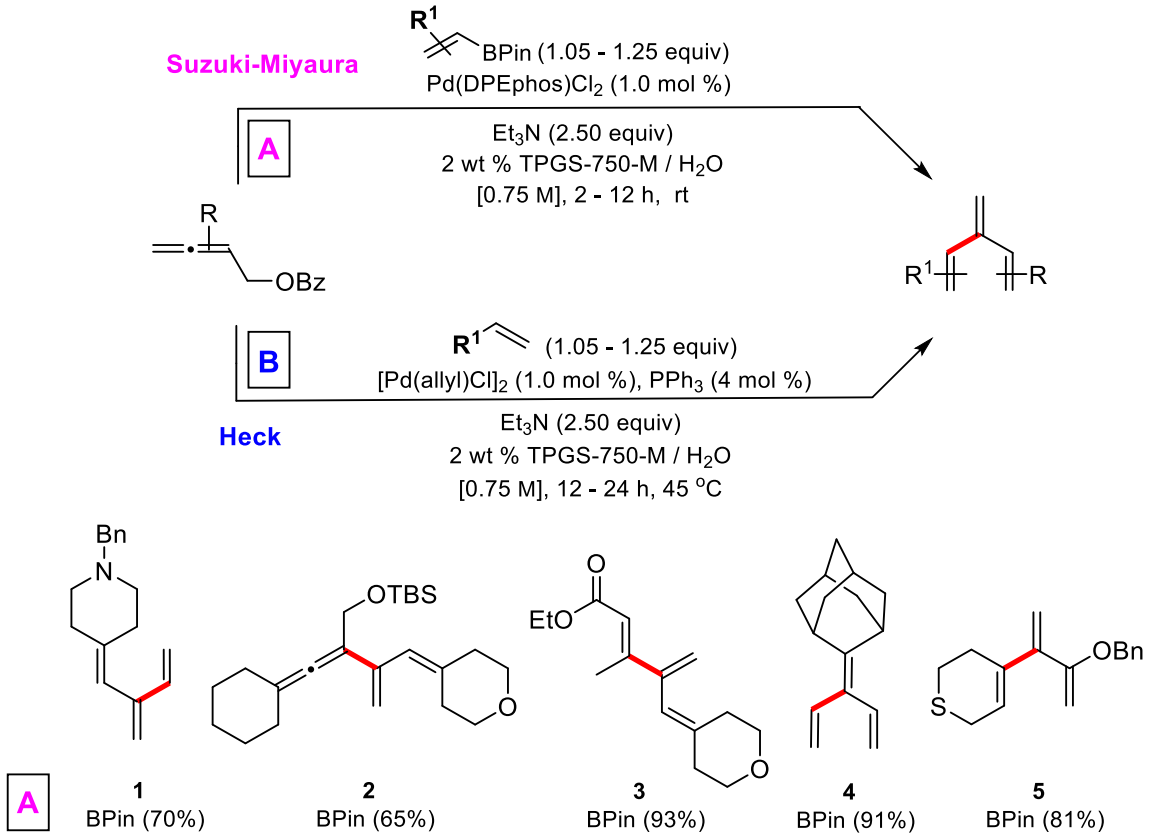
Minimal optimization was required to turn this pathway into a reliable, and good yielding, methodology for constructing symmetrical even-dendralenes. The main variable of importance was the amount of diboron reagent employed. Since, in principal, only half an equivalent is required a quick screening of 1.50, 1.25, 1.00, 0.75 and 0.50 equivalents of B_2Pin_2 (relative to mmol allene) was conducted; with greater than one equivalent leading to somewhat inferior yields, half an equivalent producing a slower reaction with less conversion, and 0.75 equivalents being the 'sweet-spot.' Indeed, a handful of selected examples of this approach are depicted in Scheme 1, leading to products **16** – **18**; novel compounds of which would be difficult to obtain by alternative synthetic techniques.

So now I knew what 'dendralenes' are, and the apparent lack of versatile and flexible inroads to access them in any regard; especially in useful and functionalized forms.

Well, given that the Suzuki-Miyaura approach to access a broad spectrum of substituted 1,3-butadienes worked so well with (hetero)aryl- boron derivatives, it was suggestive of the

potential for a route towards substituted dendralenes.[20] We thus set out to synthesize an array of various *vinyl*- boron derivatives and assess their participation under the analogous '1,3-butadiene conditions' (see Chapter I and Scheme 2, **A**).

Scheme 2. Suzuki-Miyaura Pathway to a Variety of [3]Dendralenes (A)

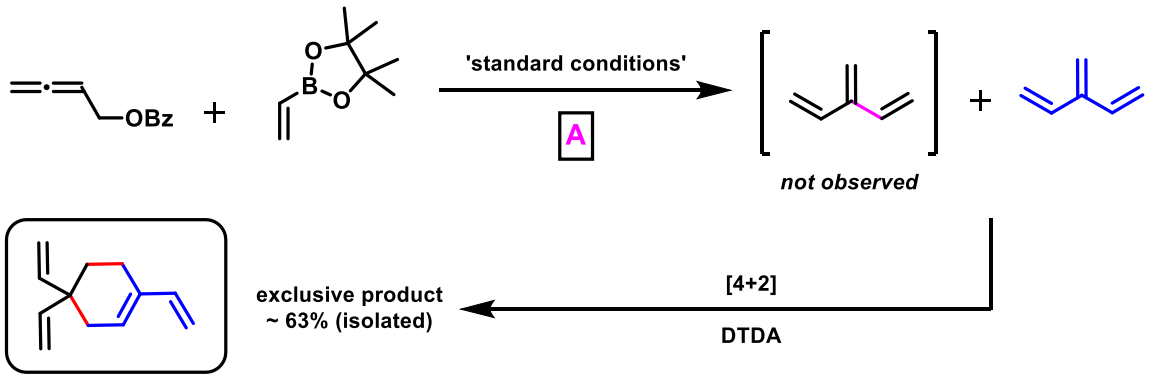


Delightfully, no issues were encountered, at all, in any of the newly synthesized *novel* [3]dendralenes; all being isolated in high yield and purity without observable instability or decomposition issues. This was of some initial surprise, since preparations of the parent family members (no substitution) appeared to be rather cumbersome; not-to-mention the elevated level of *hype* in recent literature.

That said, an investigation was undertaken to determine whether our more modern, aqueous room temperature, micellar conditions were responsible for this observed stability.

The answer was no; as shown in Figure 10, below. Although a relatively 'clean' reaction (*via* TLC analysis), upon product isolation, and NMR characterization, I quickly became aware that I had just entered a quite exclusive 'chemistry club.' *Those who've been tricked by the elusive [3]dendralene.*

Figure 10. Attempted Parent [3]Dendralene Synthesis & Observation of DTDA-Dimerization



Nevertheless, functionalities such as *N*-benzyl protected piperidines, silyl alcohols, allenes, adamantanes, thiopyrans, benzyl enol-ethers and conjugated esters smoothly engaged under the mild, aqueous, reaction conditions. These results suggest that the presence of substituents on the cross-conjugated triene framework impart sufficient stability to the products,[12] thereby leading to their facile isolation in neat form. Noteworthy is the realization of substituted enoates at either their α- or β- positions without observable isomerization.[21]

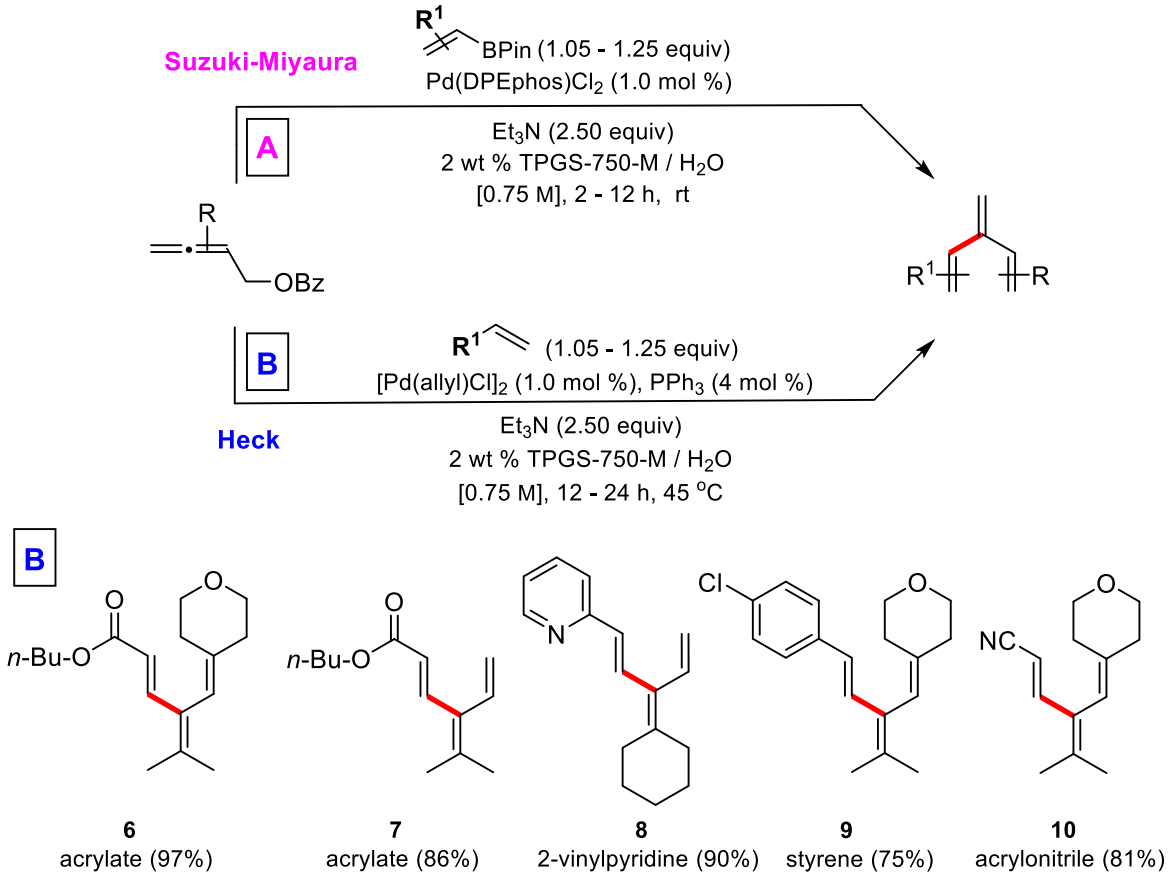
Due to the high level of success achieved in the utility of allenic esters in palladium-catalyzed cross-couplings (so far pathways **D** and **A**), we sought to gauge the efficacy of these 'hot' reagents in other, closely related, palladium-mediated reactions.

To this end, the Mizoroki-Heck (or just simply 'the Heck') reaction appeared attractive, not only due to its precedence in micellar-mediated aqueous organic chemistry,[22] but also due

to the exquisite atom economy associated with this reaction. Furthermore, this approach would help in producing products difficult to access *via* pathway **A**. A specific example of this would be β-borylated enoates which do not contain a second β- substituent (copper-catalyzed conjugate addition, of BPin, to terminal ynoates invariably gives rise to both mono- and bis-borylated adducts, accompanied with the former's respective *E-/Z-* mixture; all of which can be overly cumbersome to obtain in pure form). Thus, an effective 'Heck' would not only obviate tedious separations, but also aid in streamlining synthesis by eliminating a functionalization step (initial borylation) when compared to the analogous Suzuki-Miyaura (**A**) disconnection. Likewise; other potential reaction partners that would otherwise be difficult to amend boron onto may be realized through this 'activated-alkene' route.

Indeed, the increased electrophilicity of the *in situ*-generated π-allenyl system (see Chapter I, section 1.2), relative to an analogous π-allyl intermediate, allowed for facile reactivity with a range of activated olefins, leading to a variety of Heck-derived [3]dendralenes (Scheme 3, **B**). Thus, acrylates, acrylamides, styrenes, 2-vinylpyridine, acrylonitrile and other activated alkenes readily participated under similar micellar conditions, providing the corresponding Heck products in good isolated yields. Curiously, use of ethyl vinyl ketone as an electrophilic Heck partner led to somewhat decreased isolated yield (~ 40-50 %), accompanied with longer reaction times and potentially a side-reaction Robinson annulation pathway (not shown).

Scheme 3. Heck Pathway to a Variety of [3]Dendralenes (B)



The arrived at Heck conditions were not a simple extension of pathway **A**; they required their own ingenuity of design. Here I'd like to acknowledge my undergraduate co-worker, Michael R. Maser; who was assigned, after initial experimentation, 'the Heck.' Simple implementation of the standard conditions '**A**' were, unfortunately, not sufficient as a general and robust technology. Thus, a screening of catalysts, ligands and other reaction parameters was subsequently undertaken. The palladium salt of choice was chosen to be palladium-allyl-chloride dimer ($[Pd(allyl)Cl]_2$) due to its reliability, ease of complexation, as well as its aqueous micellar precedence in closely related Tsuji-Trost allylation chemistry.[23] Of a long list of ligands surveyed (exhaustive) it was, interestingly, observed that mono-dentate ligands

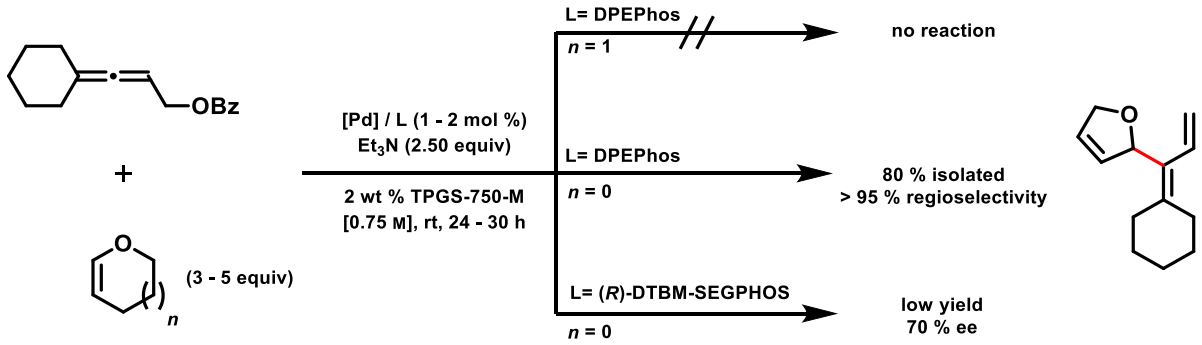
were more effective than bi-dentates, likely due to an increased propensity to dissociate, as needed, allowing for an open coordination sphere, post oxidative addition, thus allowing for coordination of the desired activated alkene. To this end, triphenylphosphine (PPh_3) was identified as the most effective, general, and accessible ligand candidate.

Other noteworthy optimizations for pathway **B** (the Heck) was the necessity for mild heating; with ~ 45 ^oC being required for ideal reactivity across all alkene classes tested. Although the reason for this is unclear at present, once the reaction mixture reaches this temperature range an obvious appearance change of the medium occurs; now providing an opaquer light orange/ yellow colored milkiness. As a side note: for other reactions of allenic esters (or cross-couplings in general) in TPGS-750-M, I've personally observed that a milky-white (to pale-white) coloration usually indicates an unreactive system. In addition, another still unsolved, and not fully understood, limitation of the Heck pathway (**B**) is the necessity of the resulting [*n*]dendralene to possess δ, δ^1-di substitution (*e.g.* for acrylate derived adducts), or *i.e.*; use of allenic esters that possess two terminal-allenic substituents.

An interesting discovery during the course of Heck experimentation was the testings of 3,4-dihydro-2*H*-pyran (DHP) and 2,3-dihydrofuran (DHF) as coupling partners, as 'activated' cyclic-alkenes. The former, DHP, led to no reaction whatsoever; even with increased reaction time, temperature, catalyst loading and so forth. This is in agreement with the scarce examples in literature, in which intermolecular Heck reactions (utilizing arylchlorides) were also negligible involving six-membered cyclic-alkenes.[24] Alternatively, in this report, ring sizes of five, seven and even eight were all equally competent. Thus, the five membered DHF was next surveyed. Pleasingly, the reaction was clean; unfortunately, it did not produce a dendralene as planned. Instead, post alkene coordination and carbopalladation/ insertion,

palladium prefers to β-hydride eliminate (~95 : 5) away from the oxygen atom (to give a directional landmark) as shown in Scheme 4. The 'net' result being a formal sp^3 C-C bond formation.

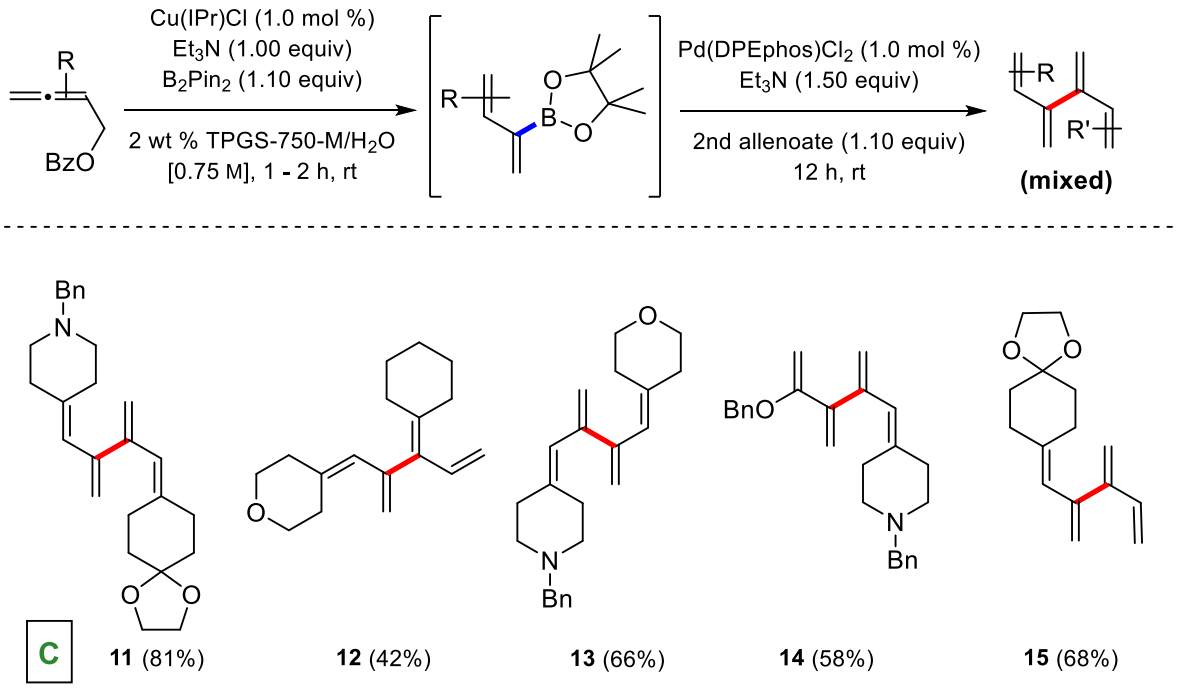
Scheme 4. Initial Results of an Intermolecular Heck-Tsuji-Trost of Allenic Esters & Asymmetric Extension



Although not the desired dendralenic derivative initially desired, the mild reaction conditions associated with micellar catalysis that efficiently effects this under-developed, yet valuable bond disconnection merited a few more experiments. As shown in Scheme 4 (bottom), employment of a non-racemically ligated palladium catalyst (in the form of (*R*)-Pd(DTBM-SEGPHOS)Cl_2) provided the desired 1,3-butadiene product with an enantiomeric-excess (% ee) of 70 %; albeit in a significantly diminished yield. It should be mentioned that this was the only chiral ligand screened thus far; and given the lack of methodologies in the literature directed at advancing the intermolecular Heck (not to mention no literature precedence for an intermolecular Heck reaction which afford *chiral* 1,3-butadienes, or [*n*]dendralenes) I believe this avenue holds considerable promise for further development in both racemic and asymmetric modes.

As mentioned earlier, initial attempts to affect a Miyaura-borylation resulted instead in homocoupling of the *in situ* derived 2-borylated-1,3-butadienes; under palladium catalysis. A report by Tsuji *et. al.*, in 2013, demonstrating precedence for copper-catalyzed borylations of closely related allenic carbonates,[25a] along with the opportunities offered by micellar catalysis for tandem reaction sequences in the same aqueous medium,[18,23] led us to pursue this route. The hypothesis was: initial carbon-boron bond formation, providing an intermediate borylated-butadiene, could be followed by a palladium-catalyzed cross-coupling, in 1-pot, furnishing [4]dendralenic derivatives of 'mixed' geometry (Scheme 5, **C**). Delightfully, borylation could be smoothly effected by employing a ligated Cu(I) salt (1.0 mol %), B_2Pin_2 (1.10 equiv), Et_3N (1.00 equiv) and an allenic ester (1.00 equiv); with the IPr-NHC (2,6-di-*iso*-propyl-*N*-heterocyclic carbene) ligand out-performing the other commonly utilized XantPhos ligand.[25b] This reaction was also so effective for its purpose that, similar to that observed for the 1,3-butadienes synthesis, a significant exotherm was often accompanied upon addition of the reaction partners such that the *outside* of the glass vial reached temperatures in excess of 41 ^{o}C!

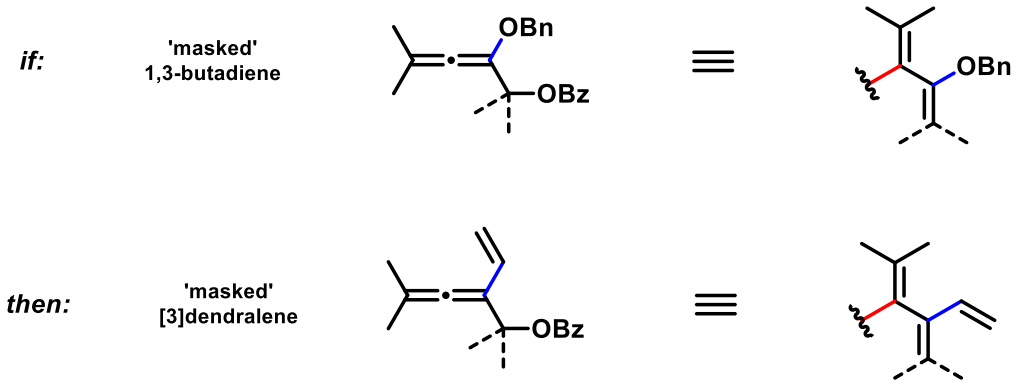
Scheme 5. Tandem Miyaura-Borylation/ Suzuki-Miyaura Sequence to Mixed [4]Dendralenes (C)



As shown in Scheme 5, this approach proved successful, furnishing a wide range of mixed [4]dendralenes **11-15**, all of which are novel molecules in every regard. Alternatively, borylation under palladium catalysis *alone* led to homocoupling of the intermediate borylated dienes, ultimately providing symmetrical [4]dendralenes **16**–**18**, *vide supra* (see Scheme 1, **D**). Of note is that homocoupling does not occur under copper catalysis even after extended reaction times (*i.e.*, from 2 to 48 h). This multi-catalytic system applied to the synthesis of dendralenes shows broad substrate compatibility, as well as functional group tolerance. Furthermore, these mild conditions compare very favorably in terms of simplicity and environmental concerns, with existing methods that typically rely upon stoichiometric organometallic reagents, excess coupling partners, and cryogenic temperatures.[1,2d,9-13,17]

With a vast array of either [3] or [4]dendralenic derivatives successfully prepared, we sought to next address the ability to access other family members of increased cross-conjugated length; by extension of the developed pathways **C** and **D**. Through retrosynthetic analysis of product [*n*]dendralenes an apparently simple disconnection was identified and targeted; as shown in Figure 11. Thus, *if* in the case of benzyl-ether substituted allenic ester, allylic transposition of the internal allenic π-bond occurs with concomitant leaving group displacement to afford 2-substituted diene adducts, with resulting 3-benzyl-ether substitution. *Then*, replacement of the benzyl-ether moiety with a vinyl group, should, instead, generate a [3]dendralene; or higher depending on the cross-coupling partner.

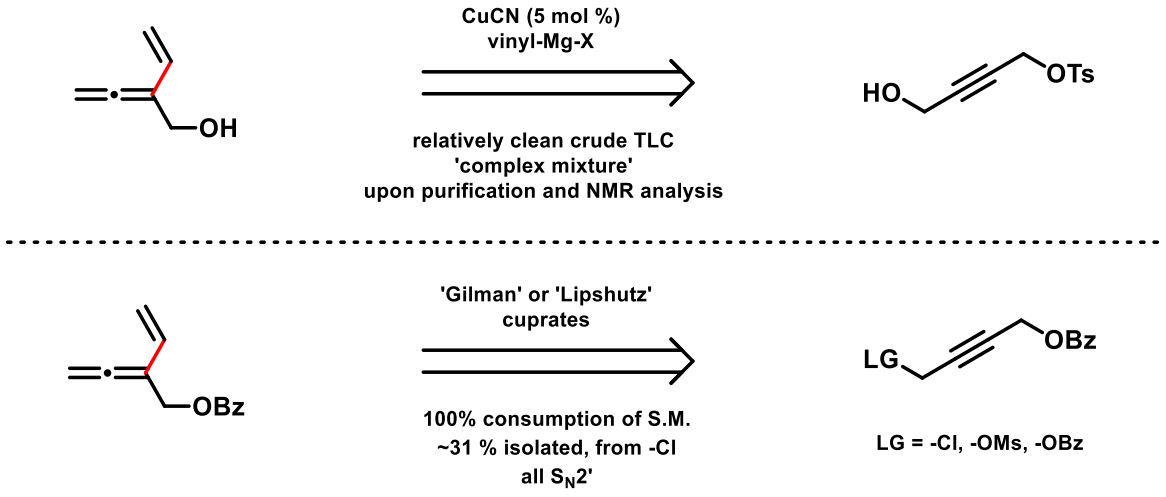
Figure 11. Retro-Synthetic Analysis to Access Higher Dendralenic Derivatives



The term '*apparently simply*' (above) was intentionally chosen, as the simplicity of the task at hand 'on paper,' was obnoxiously the opposite in the hood. Initial attempts using classical bimolecular nucleophilic substitution with allylic transposition (S_N2'[1]) conditions, employing vinyl-Grignard salts at cryogenic temperatures with the aid of catalytic (5 mol %) cuprous cyanide (CuCN) afforded, what appeared to be clean reactions *via* TLC, however in actuality, gave complex mixtures of polymeric material upon silica gel chromatography and NMR analysis (Figure 12, top). Fortuitously, a while later my lab mate, and colleague, T.

Hadley (whom had been making excellent progress with his re-surfaced -OBBD reagents, for alkyl cross-couplings *vide supra* and *vide infra*), was 'all-in' on the dendralene project and was looking for the next challenge to tackle. Together we exhaustively assessed all different variations of cuprate chemistry; from simple 'Gilman-cuprates' all the way up to mixed higher order 'Lipshutz-cuprates.'[26]

Figure 12. Retro-Synthetic Analysis to Access a Vinyl-Allenic Ester



While the approach, using mixed 'higher-order' (lithium 2-thienyl-cyano vinyl) cuprates, did produce modest quantities of vinyl-allenic ester (Figure 12, bottom), unfortunately, desired results were still to be identified to achieve higher yields, while also minimizing unproductive pathways leading to undesired and polymeric material. We had many discussions, prior to and at the time, about the obvious utility of a vinyl allenic ester; but with pressure to deliver other data-sets, I was unable to immerse myself wholly in the challenge of domesticating the vinyl-allenic ester synthesis (what I knew to be an entire notebook of research, in and of itself). Roscoe, however, was up for the task (or at least was, at first). His entry line into the situation

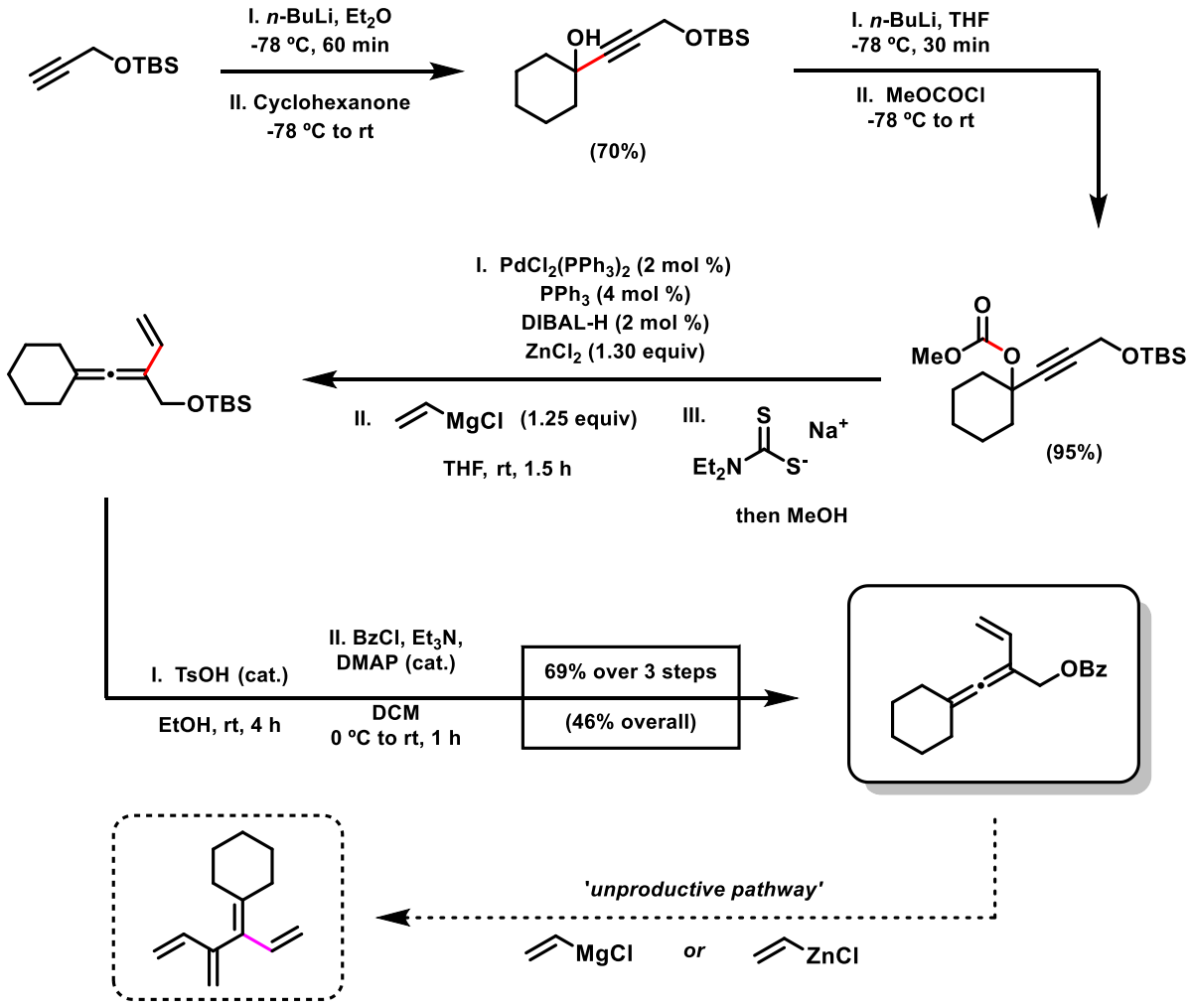
being a parody to a comment made during Sherburn's invited seminar: "Give me two weeks, and I'll give you five grams…" And so, it began.

Considering the extensive research it took to eventually arrive at an exceptionally robust synthetic route (Scheme 6), I will not attempt to describe the entire vinyl allenoate synthesis study.[27,28] I will, however, summarize some of the most prominent conclusions discerned from the experiments:

1) The best reaction examined was the Negishi cross-coupling. When compared to cuprate additions, or Kumada-type cross-couplings, with vinyl Grignard reagents, there were significantly less regioselectivity issues which can arise due to S_N2 *vs*. S_N2^1 competition.
2) Zincate reagents did not have to be pre-formed and isolated. Moreover; when formed *in situ* by transmetallation of vinyl-Grignard, from magnesium to zinc (in the form of $ZnCl_2$) a cleaner reaction profile was observed, accompanied with higher isolated yields, likely due to the unstable nature of isolated zincates (neat or in solution).
3) Surprisingly, the best ligand surveyed for this specific transformation was identified to be triphenylphosphine (PPh_3), specifically in the form of palladium-tetrakis ($Pd(PPh_3)_4$). Other catalysts/ligands screened being: $Pd(PCy_3)Cl_2$, $Pd(PPh_3)Cl_2$, Cu(IPr)Cl, Neolyst CX-31, Pd(HandaPhos)Cl_2, Pd(DPEPhos)Cl_2, and Pd(0)-(P(*o*-tol)$_3$)$_2$. Interestingly, the catalyst of choice for the methodology under development (Pd(DPEPhos)Cl_2) lead to no vinyl-allenic ester formation; instead providing exclusively unreacted starting material (~50% recovered) and the double cross-coupling adduct, the latter of which arises from initial Negishi-coupling providing the desired material, which once formed as the intermediate vinyl-allenic THP-ether (1st

generation synthesis, see note #4, below) re-enters the cross-coupling cycle preferentially, over the starting propargylic carbonate, affording an undesired [4]dendralene; in ~50 isolated yield, or ~100% relative to zinc.

Scheme 6. 2nd Generation Synthetic Route to a Representative Vinyl-Allenic Ester



4) With more labile protecting groups, such as -THP (tetrahydropyranyl), subsequent cross-coupling of the formed product into a pre-mature [4]dendralene was occasionally problematic (see note #3, above). Switching to the more robust -TBS (*tert*-butyldimethyl silyl) protecting group greatly helped to resolve this undesired issue.

5) Although $Pd(PPh_3)_4$ was identified as the most effective catalyst, its low stability to oxidation as well as the limited amount accessible to the research group at the time, made it a poor candidate for further experimentation. However, its generation *in situ* from bulk chemicals 'on-hand' was found to be quite effective at obviating these shortcomings. Thus, first, in an argon atmosphere glove-box, freshly dried zinc(II)chloride (1.30 equiv), the relatively inexpensive and far more stable $Pd(PPh_3)Cl_2$ (2 mol %) and PPh_3 (4 mol %) were weighed and, outside the glove-box, subsequently dissolved in anhydrous THF (tetrahydrofuran, ~[0.10 M]) and stirred under argon until homogenous. To this solution was slowly added, dropwise, 2 mol % (1.00 equivalent relative to palladium) of a DIBAL-H (di-*iso*-butyl aluminum hydride) solution in hexanes. Upon addition, with stirring, the resulting solution becomes deep red-to-dark brown, from the initially observed light yellow appearance; indicating reduction of palladium(II) down to the *active* palladium(0) oxidation state. Catalysts prepared in this fashion were observed to be of equal or higher activity to commercial supplies of Pd-tetrakis.

6) Although the initially pursued 'parent' (unsubstituted) vinyl allenic ester can be prepared and isolated, altering the scaffold to the terminal-cyclohexyl version imparted substantial stability of the resulting electrophilic 'masked' [3]dendralene, greatly facilitating the scaling-up of this synthetic route, and likely adding to its modest shelf-life (on the bench).

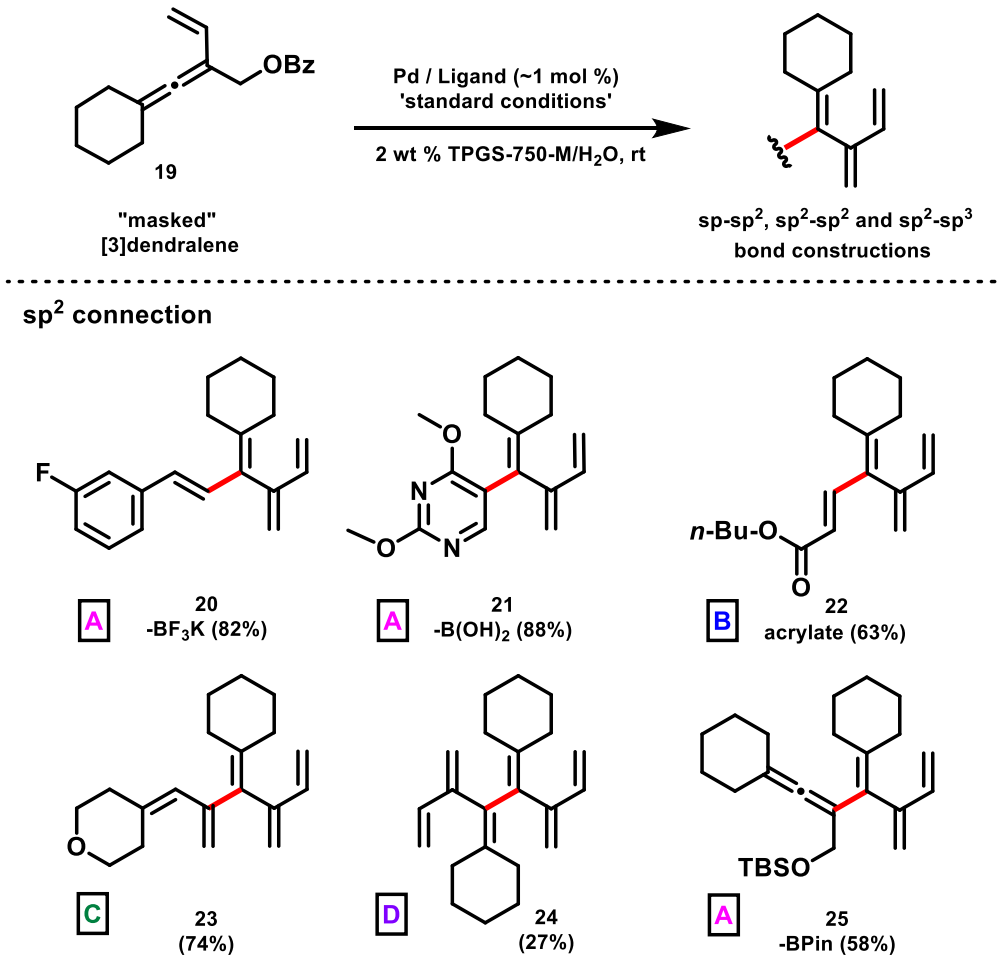
7) Lastly, and perhaps most important, is the necessity to remove, as quickly as possible, residual palladium during reaction quenching and work-up, from the crude reaction mixture. Due to the strong ability for transition metals to coordinated/ligate to π-bond-

dense systems, these metals can be 'carried-along' through subsequent chemistry, even after excessive aqueous work-up protocols, column chromatography, and even re-crystallizations. If not sequestered, then inevitable decomposition occurs, continuously, not only vastly diminishing isolated yields, but also arriving at material which, even though may be >98 % pure, is still *not* stable. Here activated charcoal was not good enough. However, a very well documented study on trace metal removal from industrial API's (advanced pharmaceutical intermediates) leading to metal contamination in the <10 ppm (parts-per-million) range, was disclosed around the same time our issues were arising.[29] Their technique centered around dithiocarbamates, as universally strong and robust chelating agents, in which nearly any metal can be efficiently sequestered (*e.g.* Cu, Rh, Ru, Pd, Ni, *etc.*) regardless of oxidation state. Thus, upon quenching the reaction with the appropriate amount of methanol, followed by brief stirring, NaDEDTC (sodium diethyldithiocarbamate trihydrate) is introduced in one portion, stirred, allowed to settle, and filtered.[27,28] This process was then repeated, after concentration of the volatiles *en vacuo*, on the filtrate at least once more.[30]

With an ample supply of this representative vinyl-allenic ester (**19**), initial test experiments were next undertaken to evaluate its reactivity under the standard reaction conditions **A** – **D**, relative to that observed with analogous 'simple' allenic esters (lacking this 'vinyl' appendage). Remarkably, by altering the electrophilic coupling partner to vinyl allenoate **19** (Scheme 7) not only were all the reaction conditions (pathways **A** – **D**) amenable but reactions

were actually faster in most cases; highlighting the *even higher* electrophilicity of this educt relative to simple allenic esters.

Scheme 7. 'Higher' Unsymmetrical Dendralenic Derivatives *via* a Vinyl-Allenic Ester (1)

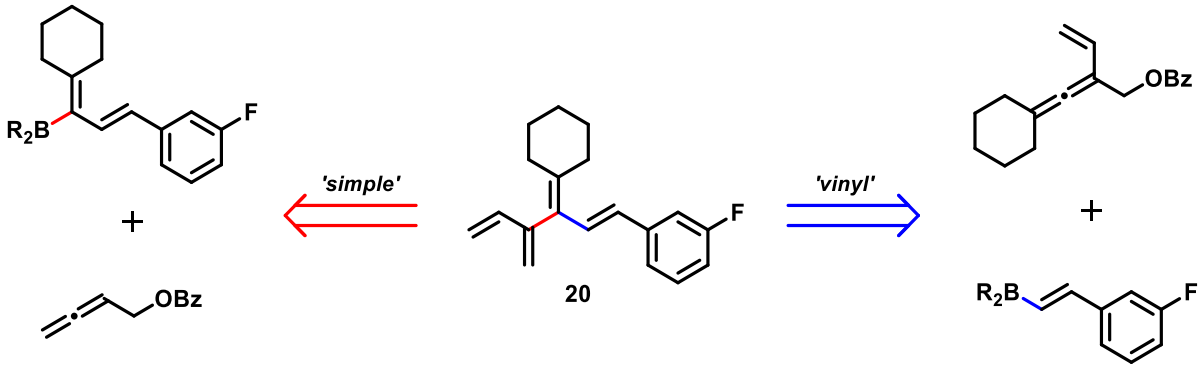


The success of this hypothesis thus provided rapid entry to substituted [3], [4], [5] and [6]dendralenes. Accordingly, the Suzuki-Miyaura vinyl-coupling approach (**A**) could now be exploited to access [4]dendralenes **20** and even product **25**, the latter of which represents the *first* reported synthesis of a '[4]allenic dendralene' in all of the chemical literature. Similarly, use of more standard heteroaryl boron species smoothly produced [3]dendralene **21** in an uneventful fashion. Employing the Mizoroki-Heck conditions (**B**) with *n*-butyl acrylate

furnished the extended Michael [4]dendralene **22**, containing unsaturated carbonyl functionality for further elaboration. Satisfyingly, both pathways **C** and **D** proved to be valid approaches towards **19**, thereby constructing the more difficult C-C bonds of mixed [5]dendralene **23** and symmetrical [6]dendralene **24**. The novel molecules showcased in Scheme 7 would be understandably difficult to access by alternative synthetic methodologies.

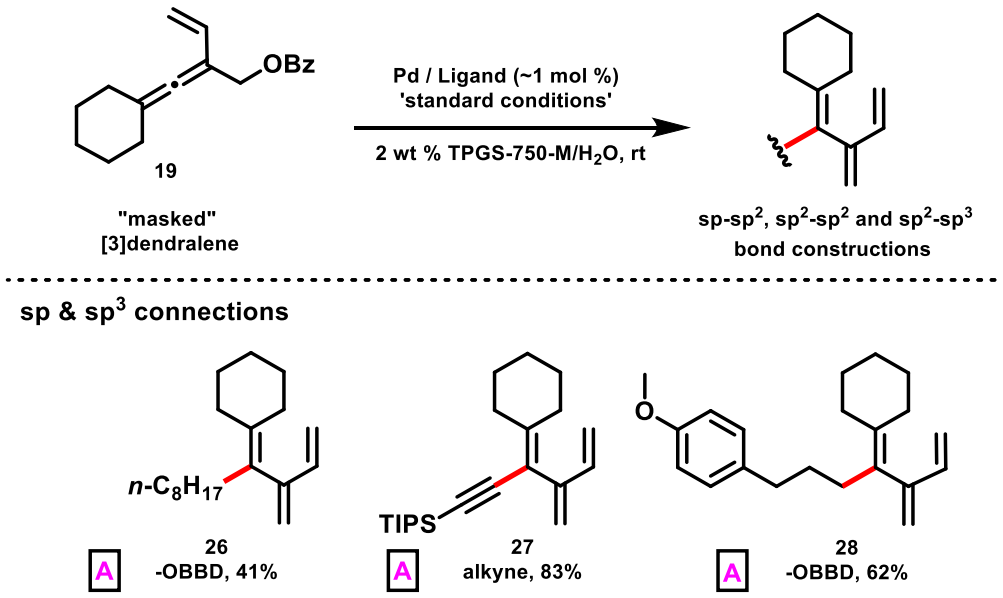
Of particular note is the ability of this representative vinyl allenoate to serve as a masked [3]dendralene, providing an alternative bond disconnection relative to that found in allenoates lacking this alkenyl appendage (Figure 13).

Figure 13. Alternative Bond Disconnections: Simple *vs.* Vinyl Allenes



For example, looking at the potential bond disconnections for adduct **20,** under the standard Suzuki-Miyaura conditions (**A**) two situations arise. Without access to a vinyl allenic ester, two butadiene moieties would need to come together *via* parent allenic benzoate and a 2-borylated butadiene (Figure 13, red bonds, left), the latter of which may be challenging or multi-step-requiring to obtain. Conversely, when employing a vinyl allenic benzoate the more readily available β-borylated styrene derivative can be utilized (Figure 13, blue bonds, right) to affect the same 'net' product.

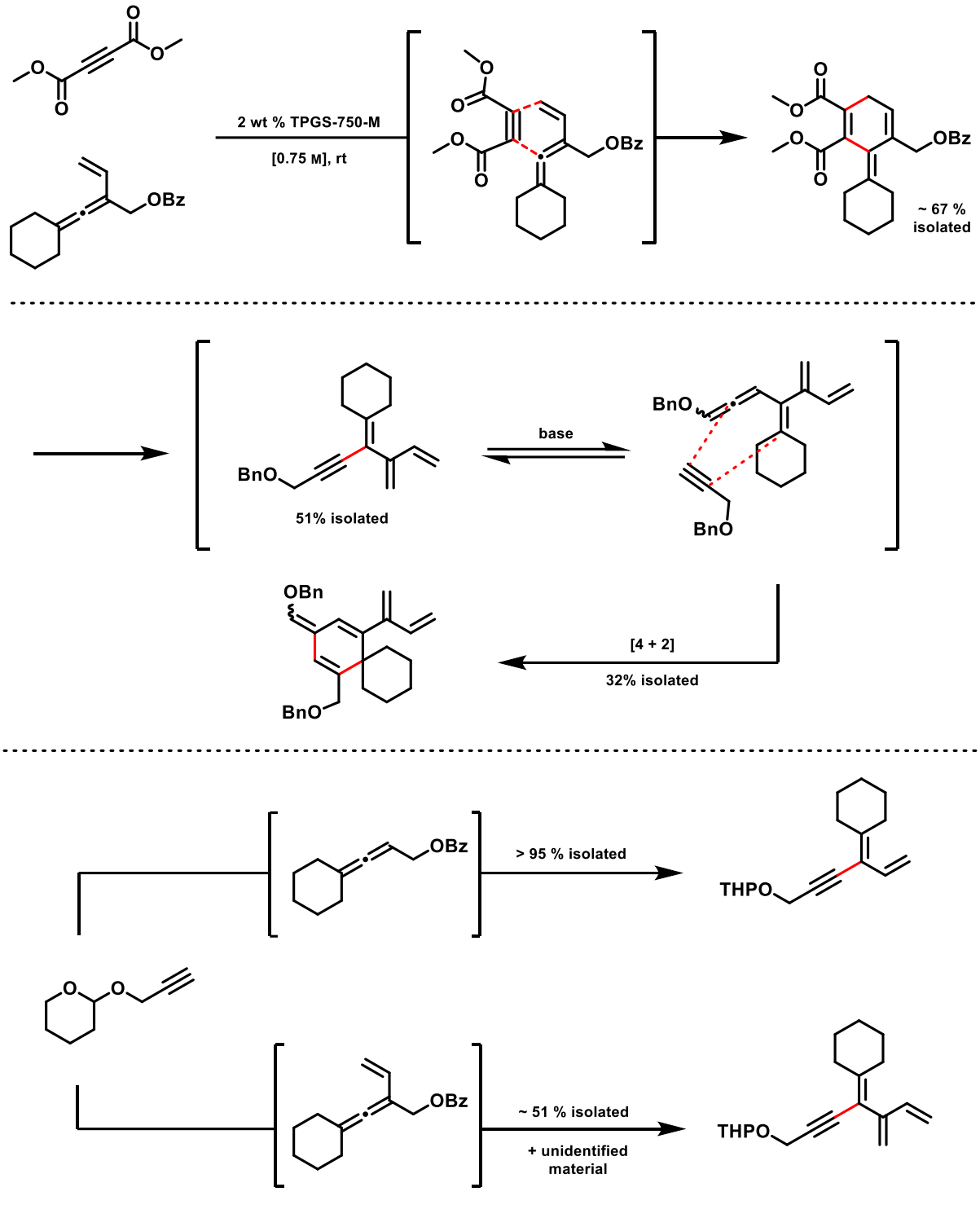
Scheme 8. 'Higher' Unsymmetrical Dendralenic Derivatives *via* a Vinyl-Allenic Ester (2)



Furthermore, the Suzuki-Miyaura approach '**A**' could be extended beyond sp^2-sp^2 couplings to include sp-sp^2 and sp^2-sp^3 bond formations (Scheme 8). Underutilized 'OBBD' (9-oxa-10-borabicyclo-[3.3.2]decane) *borinate* derivatives, as an intermediary between boronic acids (less reactive, more stable) and boranes (more reactive, less stabile), engaged readily with **19** leading to **26** and **28** in acceptable isolated yields.[27,31] As well, bulky TIPS-acetylene (ethynyl tri*iso*propyl silane) coupled readily with **19** leading to **27**.[18,32] The success of this Sonogashira coupling reaction was in large measure due to the steric effects of the acetylene coupling partner, thereby shielding the triple-bond from being able to associate with the cumulated diene and participate in an undesired [4 + 2] cycloaddition.

Indeed, with other, less bulky, acetylenes this was observed. Even in the absence of catalyst, *i.e.* upon stirring a 1:1 mixture of **19** and DMAD (dimethyl acetylene dicarboxylate), in aqueous TPGS-750-M at room temperature, the DTDA product was rapidly formed; and in short reaction time (Figure 14, top); indicative of the high π-density about the vinyl allene framework.

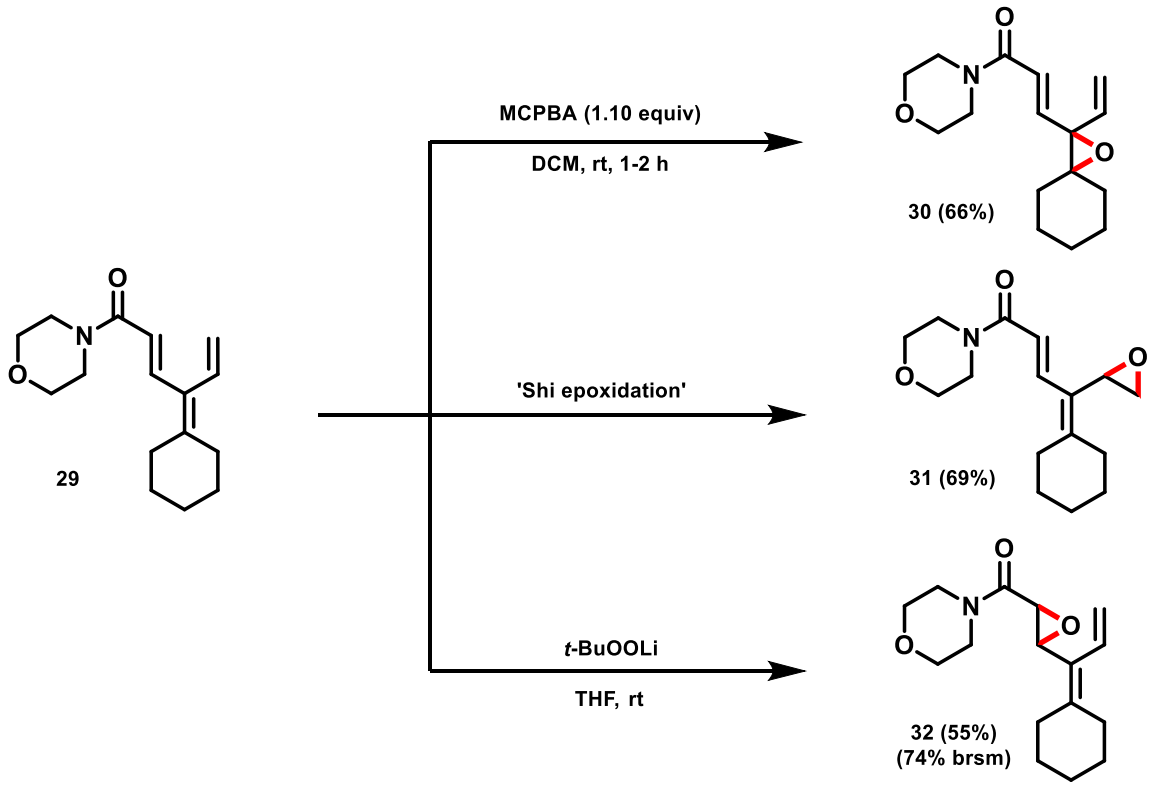
Figure 14. Observation of Uncatalyzed [4 + 2] DTDA & Proposed Rearrangement Chemistry of Propargyl Adducts



As well, with protected propargyl alcohol derivatives these two pathways (Sonogashira *vs*. DTDA) were shown to be in competition with one another, as well as a third pathway. This third case (Figure 14, middle) was an initial Sonogashira-type coupling, followed by subsequent base catalyzed isomerization of the propargyl group into an allenyl-ether moiety, which in turn engages with yet another molecule of acetylene *via* a different DTDA pathway. This was attributed to the high local π-density of the propargylic-[3]dendralene; as the corresponding propargyl-butadiene-equivalent displayed no such alternative pathways, being isolated in > 95% (Figure 14, bottom).

Part of the incentive to develop inroads to unsymmetrical dendralenes lies in the potential for regioselective functionalization of the multiple olefinic sites within such molecules, well beyond their current utility in DTDA sequences. In this regard we sought to demonstrate the true potential of the cross-conjugated framework of dendralenes by exploiting their ability to orthogonally engage in synthetically useful reactions. To this end we chose to embark on identifying conditions for site-selective epoxidations; which are arguably among the most important and useful synthetic-handles for further chemical elaboration. As illustrated in Scheme 9, site selective epoxidation furnished products **30** - **32** resulting from exclusive reaction at one of the three possible olefinic sites in representative [3]dendralene **29**.[33]

Scheme 9. Regioselective Epoxidations of Unsymmetrical [3]Dendralene 29

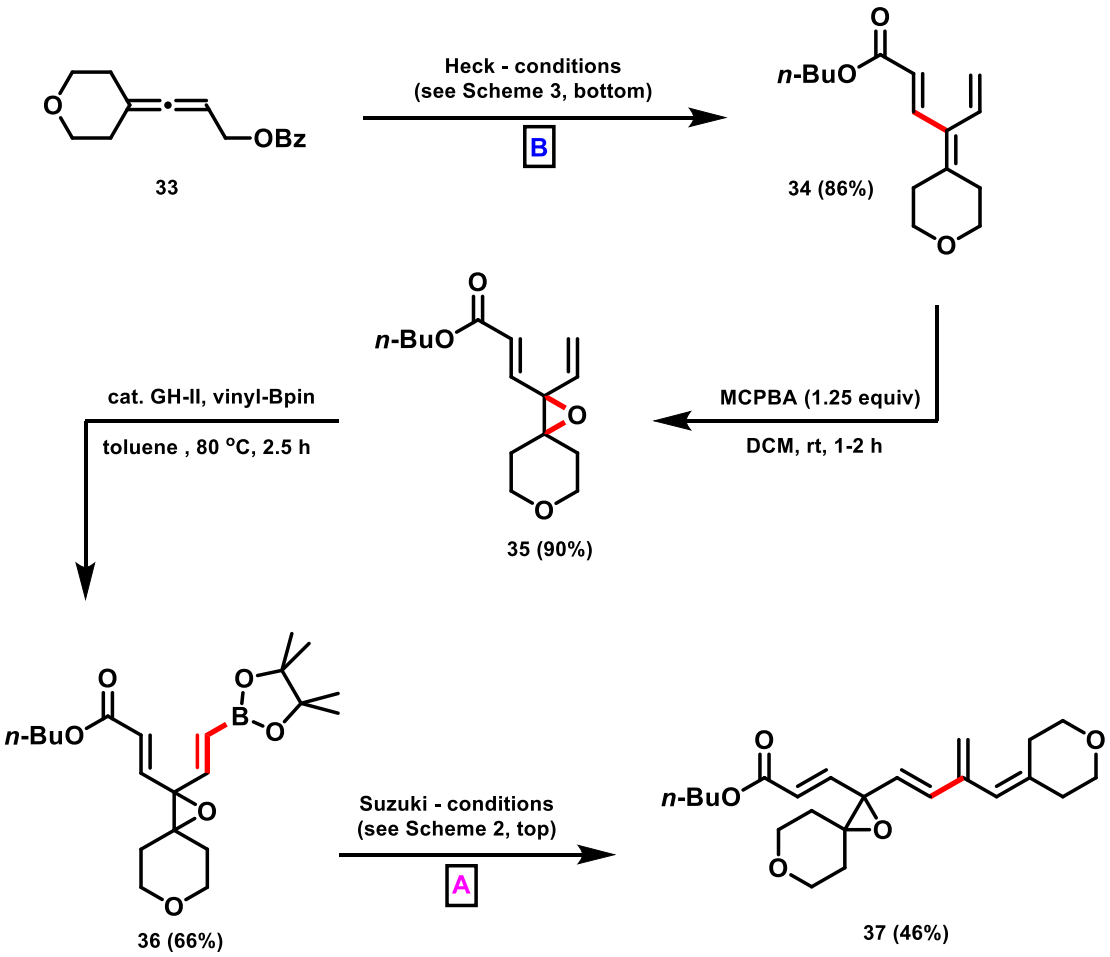


First, classical reaction conditions employing MCPBA (*meta*-chloroperoxybenzoic acid), an electrophilic epoxidizing reagent, was surveyed.[33a] Gratifyingly, the reaction was perfectly selective, regio-selectively epoxidizing the central, most electron rich, tetra-substituted olefin (Scheme 9, top) as expected, leading to product **30**. To oxidize the terminal, vinylic, olefin it was envisioned that Shi's protocol, which has been shown to be most reactive toward least substituted, most accessible, olefins, would be amendable.[33b-d] Initial experiments, following Shi's various adjustments for catalytic epoxidations using a solvent-cocktail system *did* give exclusive regio-selectivity; however, in very low yields and mainly unreacted starting material. By augmenting the solvent system to an acetonitrile-water mixture and omitting the addition of DMM (dimethoxy methane), as well as increasing the loading of the fructose derived 'Shi

reagent' (from 30 mol % to 1.25 equivalents), good isolated yields of terminal olefin epoxidations (*e.g.* **31**) were achieved; without compromising the overall exclusivity for site selectivity (Scheme 9, middle). Lastly, epoxidation of the α,β- position of the unsaturated morpholino amide, in Michael [3]dendralene **29**, was achieved *via* nucleophilic conjugate addition of lithiated *tert*-butyl hydroperoxide. Thus, initial β-attack of the nucleophilic peroxy-group, followed by intramolecular α-attack of the resulting enolate, directly, and selectively, afforded the desired epoxide **32** (Scheme 9, bottom).[33e] Surprisingly, attempts to effect an alcohol directed epoxidation (*i.e.* 'Sharpless' conditions after initial reduction of the ester or amide to the corresponding primary allylic alcohol) led to either no reaction or isolation of aldehydes; the latter of which being the result of an unforeseen alcohol oxidation, without any detectable observation of 'Sharpless-epoxidation' products. Nevertheless, in each successful case (*i.e.* adducts **30** – **32**), differentiated dienic functionality remains in the product (*e.g.* 1,3-butadiene, skipped-diene, Michael acceptor, epoxide, vinyl, carbonyl, Weinreb amide equivalent, *etc*.), thereby creating numerous opportunities for further elaboration.

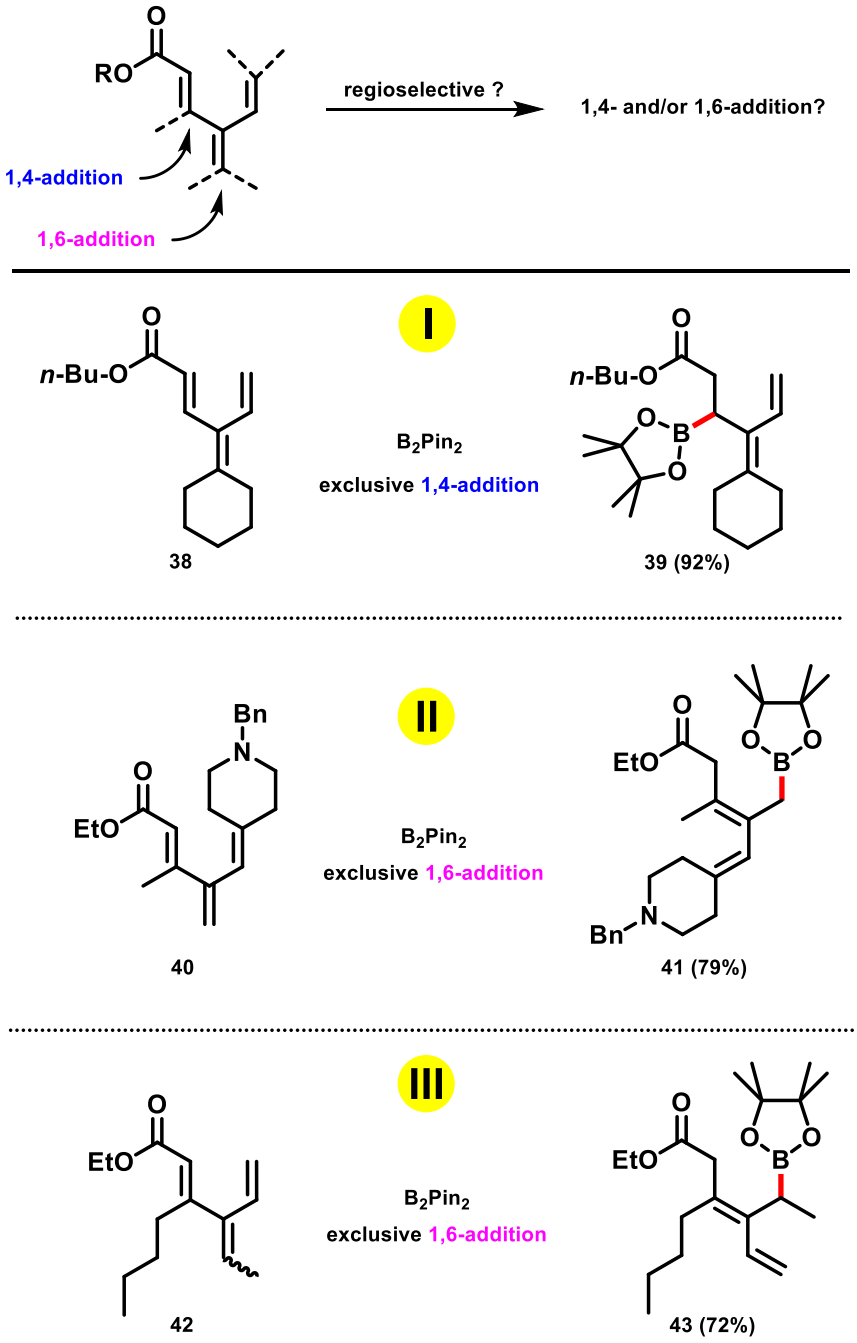
For example, conversion of educt **33** to [3]dendralene **34**, followed by Henbest epoxidation afforded terminal olefin **35** (Scheme 10). Grubbs-Hoveyda-II-catalyzed cross-metathesis afforded the corresponding vinyl boronate **36**,[34] which is well-positioned for further use *via* yet another cross-coupling, represented by the synthesis of new [3]dendralene **37**.

Scheme 10. Synthetic Route to Highly Functionalized [3]Dendralene 37



Likewise, introduction of conjugated carbonyl functionality, as present in educts **38**, **40**, and **42** (Scheme 11), sets the stage for either future 1,4- or 1,6-additions. Copper-catalyzed addition of BPin[35] to Michael-[3]dendralenes, each bearing a different substitution pattern (cases **I** - **III**), led exclusively to products **39**, **41**, and **43**, respectively, suggestive of the dominance of steric effects in controlling the outcome of these conjugate additions.

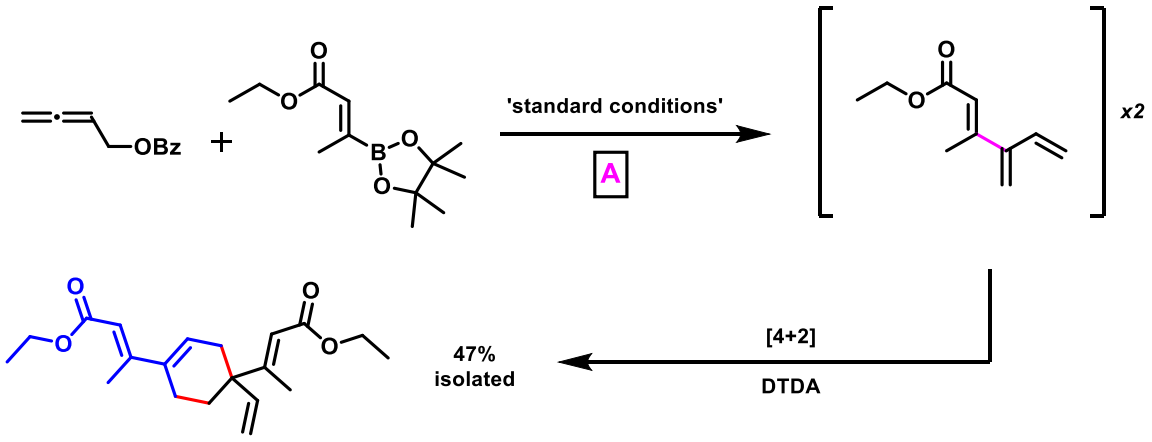
Scheme 11. Regioselective 1,4- and 1,6-Additions to Michael-[3]Dendralenes



In case **I**, delivery of BPin occurred at the expected, sterically most favorable β-site. With β,β^1-disubstitution, however, copper adds at the unhindered δ-position (case **II**) affording the

(*E*)-1,6-borylated adduct. Increasing the extent of substitution in case **III** still favors 1,6-addition over the fully substituted β-site. With both the β- and δ-positions disubstituted, little to no borylation was observed (see experimental section for a [1,4]-CuH approach, *ca.* 9%). Thus, it appears that Cu-catalyzed Michael additions to [3]dendralenes follow similar patterns of reactivity as seen in traditional cuprate additions to unsaturated systems. It should be noted that in attempts to synthesize a Michael-[3]dendralene unsubstituted at the δ-position, and also unsubstituted at the terminal olefinic site, led instead to isolation of the interesting DTDA-dimer shown in Figure 15; likely due to a combination of high polarization and lack of steric shielding.

Figure 15. Yet Another…Unexpected DTDA-Dimerization



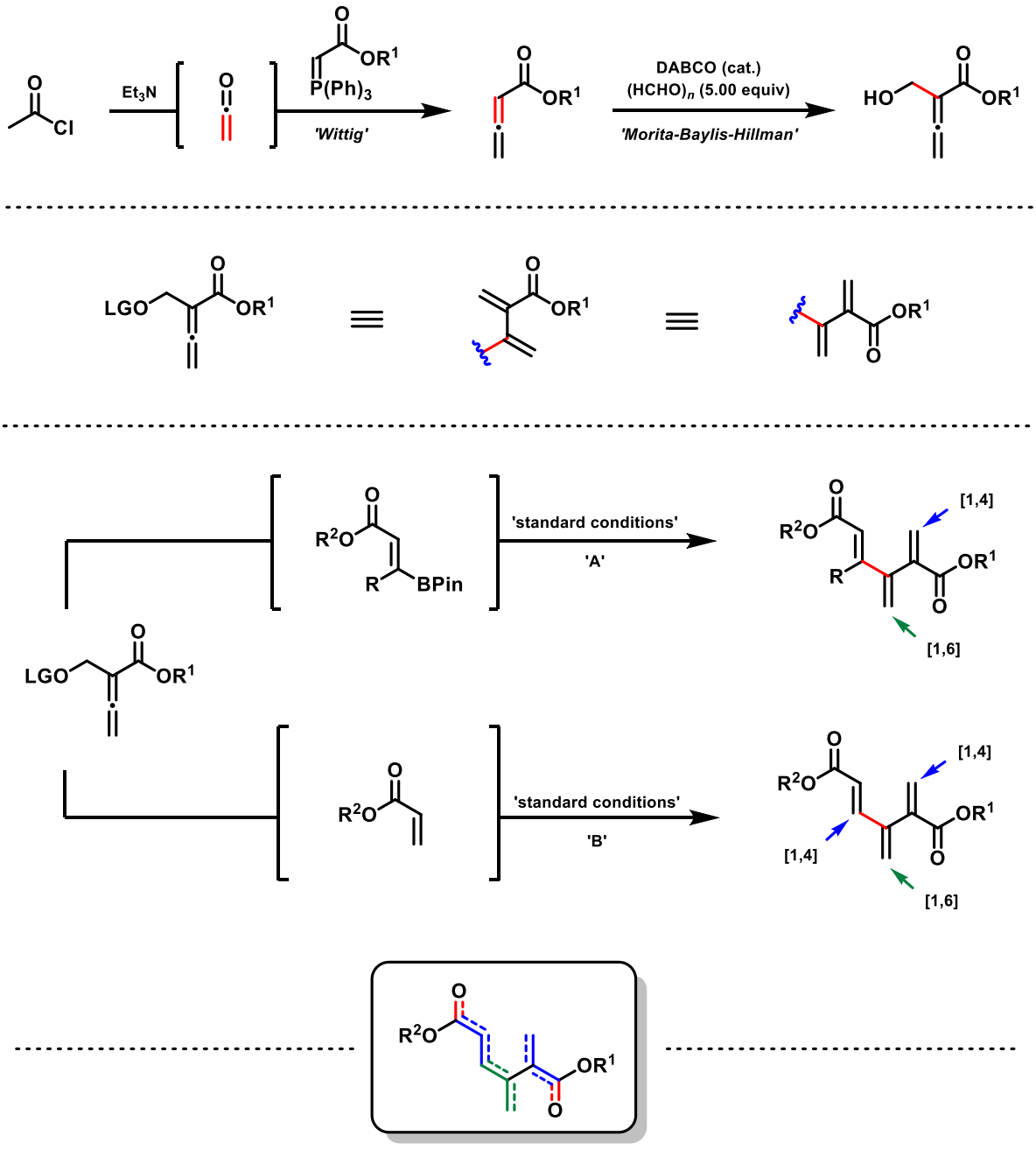
Given the magnitude of parity-dependence, especially between the smallest [3] and [4]dendralenic derivatives, it would be interesting to observe the selectivities and reactivities of the [4]dendralenic equivalents of educts **38**, **40**, and **42**. Perhaps these too would arrive at similar outcomes; or perhaps they exhibit alternative, and unique, modes of action in conjugate addition reactions due to their *even*-dendralenic properties.

2.3. Miscellaneous Discoveries / Future Curiosities

Other research endeavors, as extensions to the successful work described herein, centered around curiosity. Two, of the many, I'd like to mention. Perhaps for their potential utility in chemical synthesis, or perhaps simply out of the stimulating questions that may surface if pursued.

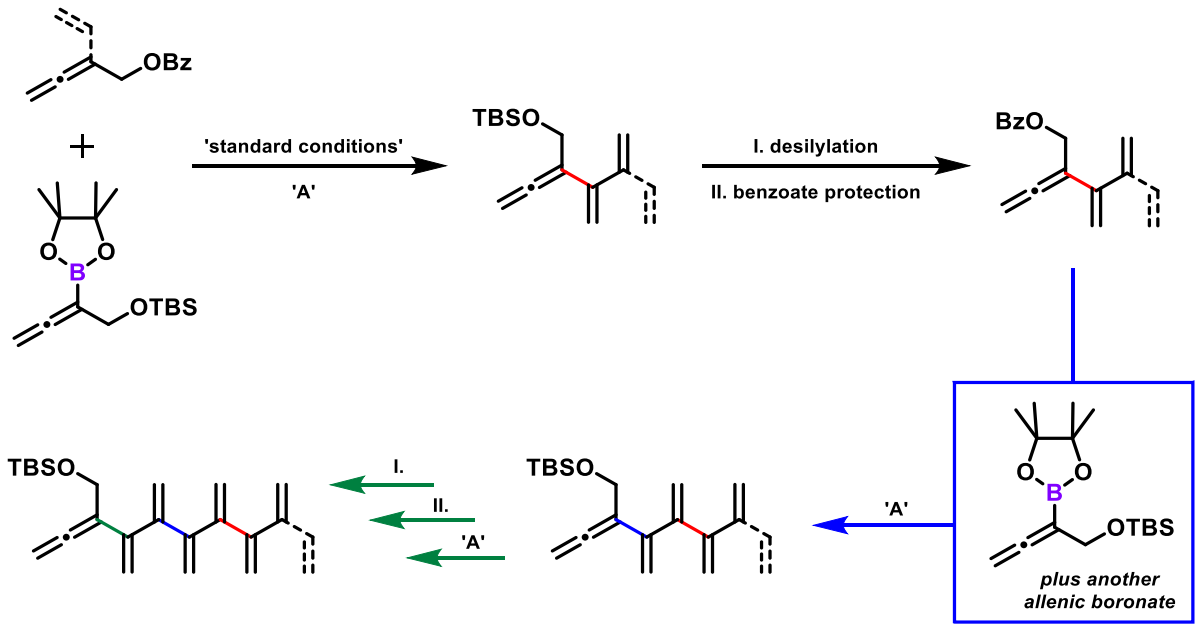
Firstly, stimulated by the exclusivity observed in copper-catalyzed conjugate addition reaction of Michael-[3]dendralenes, which appeared to reliably follow classical conjugate additions rules in regard to *steric effects*, the question of potential *electronic effects* was still left unanswered, due in part to the difficulty in obtaining test substrates containing both unsubstituted β- and δ-sites (or even mono-β only substituted). Thus, if accessible, the ideal test molecule would contain both possibilities of 1,4- or 1,6-addition; both of which would not be affected by steric bias. By utilizing this single molecule approach, the question of electronic influence can then be properly addressed (Figure 16). Furthermore; the uniqueness of these organic frameworks would most likely breed new and interesting chemistry in and of itself. Especially when evaluating the many possibilities associated with any of the many possible enolate intermediates, toward either intra- and inter-molecular cascade processes.

Figure 16. Applications of a Multi-Michael-Acceptor-[3]Dendralene



Secondly, from the viewpoint of dendralene synthesis, a potential extension of the work described herein to access even higher dendralenic oligomers would revolve around further manipulation of adducts **2** (Scheme 2) and **25** (Scheme 7), 'allenic [3] and [4]dendralenes;' respectively. These products are well configured to iteratively elongate/ extend the cross-conjugated 'back-bone,' as desired.[36]

Figure 17. Iterative-Cross-Coupling of Allenyl Boronates & Allenic Esters



This is envisioned to be possible through initial exchange of the primary alcohol's protecting group for an appropriate leaving group (*e.g.* the corresponding benzoate) resulting in butadienyl- or [3]dendralenyl-allenic esters (Figure 17). This ICC (iterative-cross-coupling) approach to cross-conjugated systems synthesis, in theory, can provide any length and substitution pattern desired for any given theoretical [*n*]dendralene.

2.4. Conclusion

In conclusion, new technology has been developed that provides inroads to variously substituted [3]-[6]dendralenes. Key features highlighted herein include: (1) the advantages of micellar catalysis, in particular the environmentally responsible nature of these key Suzuki-Miyaura/ Heck coupling reactions being performed in the complete absence of organic solvents; (2) the use of a vinyl allenic benzoate as a 'masked' [3]dendralene; (3) the unified approach to a range of substituted dendralenic oligomers from a common synthon; (4) first time access of the [4]allenic-dendralene framework; (5) the proclivity of these novel dendralenes towards regioselective further functionalization; and (6) their ready participation as educts in several important synthetic transformations. In the composite, the research described herein is representative of an area of fundamental research that remains, in large measure, surprisingly unexplored, especially with regard to exciting applications to various targets in synthesis, and natural products in particular.

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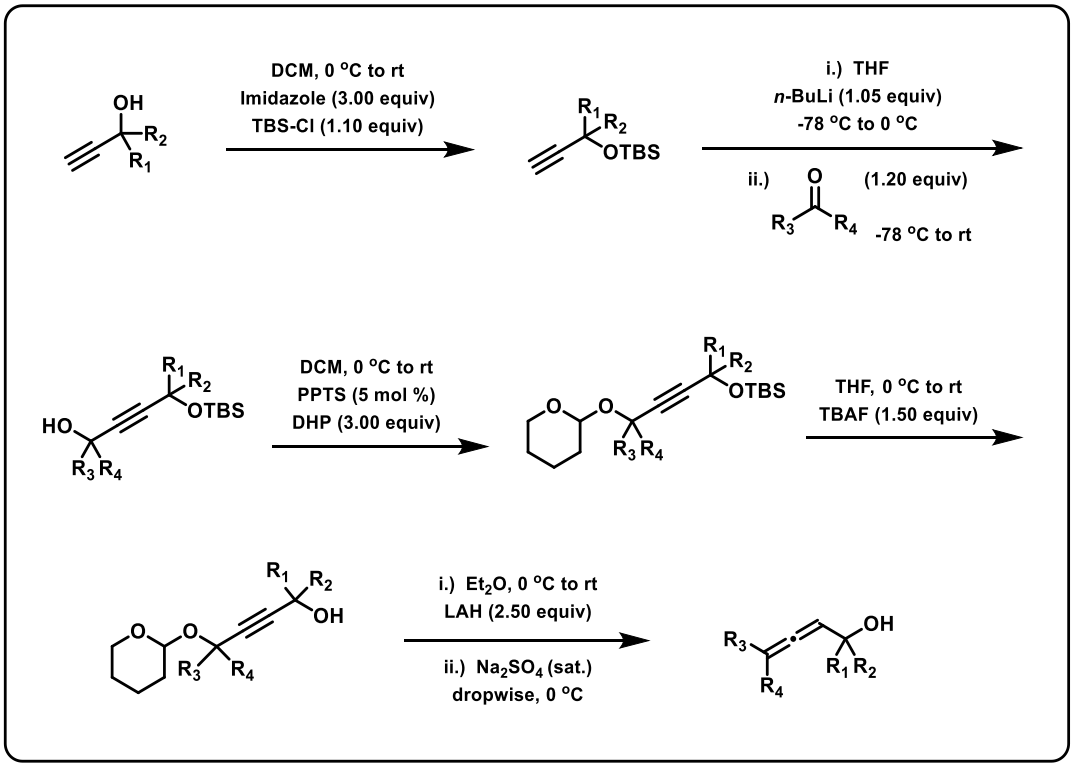
2.6. Experimental Data

1. Synthetic Details

1.1 Synthesis of allenic intermediates

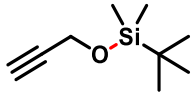
Many reliable synthetic routes have been developed to prepare substituted allenes. A few of these classical techniques involve transformations similar to those utilized in this research. Access to more complex and distinct allenic substrates however, necessitated the development of *new* chemical procedures that involved novel precursors as well as unknown reaction adducts. The chemical syntheses are detailed below.

Route 1: [2]



***tert*-Butyldimethyl(prop-2-yn-1-yloxy)silane**

Notebook: DJL-2-225, DJL-4-186/206/219, DJL-6-046



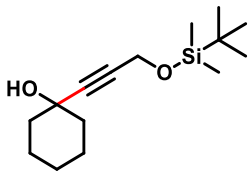
To a RBF charged with a magnetic stir bar and dry DCM, ~ [0.50 M], was added propargyl alcohol and the resulting solution was brought to 0 °C with stirring. Once at 0 °C, imidazole (3.0 equiv) was added in one portion and the mixture was stirred for ~10-15 min (until the base was fully dissolved). Then, TBS-Cl (1.10 equiv) was introduced, in one portion, and the reaction was allowed to warm to rt overnight. Once the reaction was complete *via* TLC analysis (see below), the stir bar was removed from the RBF and the mixture was concentrated to about 1/8 its volume *via* rotary evaporation. The resulting crude oil was loaded onto a silica gel column with subsequent hexane washes to assure quantitative transfer, leaving the residual salts in the RBF. The product was purified *via* column chromatography on silica gel, eluting with 3% (ether : hexanes), to obtain the title compound as a colorless oil, 94% isolated.

TLC: R_f = 0.60 (5% ether : hexanes), $KMnO_4$

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.13 (d, 2H), 2.35 (t, 1H), 0.91 (s, 9H), 0.13 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 82.6, 72.9, 51.7, 25.9, 18.4, -5.1

1-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-yn-1-yl)cyclohexan-1-ol



To a RBF charged with a magnetic stir bar and dry THF, ~ [0.25 M], was added the alkyne, and the resulting solution was brought to -78 °C with stirring. Once at -78 °C *n*-BuLi

(~[2.25 M] in hexanes; 1.05 equiv) was added dropwise, and this mixture was then stirred for ~ 30-45 min at -78 ^{o}C and then ~ 30 min at rt. After that time, the solution was again brought to -78 ^{o}C and a solution, ~ [1.0 M], of the desired ketone in dry THF was added dropwise and allowed to stir overnight (~ 8-12 h). Once the reaction was complete *via* TLC analysis (see below), it was quenched with saturated aqueous ammonium chloride, followed by transfer to a separatory funnel containing DI water and diethyl ether. Extraction with ether (x 3) followed by drying of the organic layers with anhydrous Na_2SO_4, salt filtration and subsequent concentration *via* rotary evaporation provided the crude material which was then subjected to column chromatography on silica gel, eluting with 20% (ether : hexanes) to obtain the title compound as a white solid, 89% isolated.

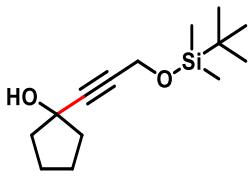
TLC: R_f = 0.38 (20 % ether : hexanes), UV, I_2, vanillin stain (blue spot)

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.07 (dd, *J* = 5.2, 1.2 Hz, 1H), 4.36 (s, 2H), 3.96-3.90(m, 1H), 3.49-3.44 (m, 1H), 2.00-1.97 (m, 1H), 1.85-1.80 (m, 2H), 1.72-1.56 (m, 6H),1.55-1.46 (m, 6H), 1.28-1.20 (m, 1H), 0.89 (s, 1H), 0.11 (s, 6H)

^{13}C NMR: (100 MHz, $CDCl_3$) δ 96.0, 86.2, 84.7, 75.2, 63.8, 51.9, 38.9, 38.5, 32.3, 29.9, 25.6, 25.4, 20.8, 18.4, -4.9

1-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-yn-1-yl)cyclopentan-1-ol

Notebook: DJL-2-125, DJL-4-208



Purification: column chromatography on silica gel eluting with 10% (ether : hexanes), white solid, 78%.

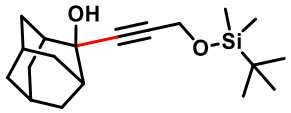
TLC: R_f = 0.45 (10 % ether : hexanes), UV, I_2, vanillin stain (blue spot)

^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.35 (s, 2H), 2.04 (br. s, 1H, OH), 1.89-1.82 (m, 2H), 1.72-1.59 (m, 2H), 1.58-1.46 (m, 4H), 0.90 (s, 9H), 0.12 (s, 6H)

^{13}C NMR: (100 MHz, $CDCl_3$) δ 88.6, 81.9, 74.6, 51.9, 42.4, 26.0, 23.5, - 4.9

(1*S*,2*R*,5*R*)-2-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-yn-1-yl)adamantan-2-ol

Notebook: DJL-4-188



Purification: column chromatography on silica gel eluting with 15% then 20% (ether : hexanes), white solid, 98%.

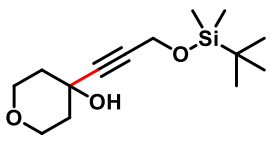
TLC: R_f = 0.45 (30% ether : hexanes), UV, I_2, vanillin stain (crimson spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.39 (s, 2H), 2.14 (m, 4H), 1.92 (m, 2H), 1.82-1.73 (m, 4H), 1.72-1.67 (m, 3H), 1.58-1.53 (m, 2H), 0.95 (s, 9H), 0.12 (s, 6H)

^{13}C NMR: (125 MHz, $CDCl_3$) δ 89.3, 83.4, 72.6, 52.0, 38.9, 37.7, 37.1, 35.5, 34.8, 33.1, 31.7, 27.0, 26.9, 25.9, 18.4, -4.9

4-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-yn-1-yl)tetrahydro-2*H*-pyran-4-ol

Notebook: DJL-5-295



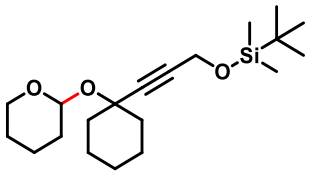
Purification: column chromatography on silica gel eluting with 10% then 25% (ether : DCM), clear colorless oil, 92%

TLC: R_f = 0.31 (20% ether : DCM), UV, I_2, vanillin stain (forest green spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.37 (s, 2H), 3.93 – 3.83 (m, 2H), 3.65 (m, 2H), 2.20 – 2.06 (m, 1H), 1.97 – 1.87 (m, 2H), 1.79 (m, 2H), 0.92 – 0.88 (m, 9H), 0.15 – 0.04 (m, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 87.1, 83.8, 64.9, 51.8, 40.0, 25.9, 18.4, 15.4, -4.9

tert-Butyldimethyl((3-(1-((tetrahydro-2*H*-pyran-2-yl)oxy)cyclohexyl)prop-2-yn-1-yl)oxy)silane



To a RBF charged with a magnetic stir bar and dry DCM, ~ [0.50 M], was added the alcohol and the resulting solution was brought to 0 °C with stirring. Once at 0 °C, catalytic PPTS (pyridinium *p*-toluenesulfonate, ~ 2-3 mol %) was added in one portion and the mixture was stirred for ~10-15 min. Then DHP (1.50 – 2.00 equiv) was introduced dropwise and the reaction was allowed to warm to rt overnight (~12 h). Once starting material was fully consumed (usually within 2 h; however, extended reaction time doesn't affect the reaction mixture) *via* TLC analysis (see below), the reaction was diluted with DCM and quenched with solid K_2CO_3. The resulting mixture was then passed through a plug of Celite / sand / Celite / sand (the extra layers of sand help to gather unwanted salts and DHP promoted polymeric material). After concentration *via* rotary evaporation the resulting crude oil was loaded onto a silica gel column with minimal hexanes to assure quantitative transfer, eluting with 5% (ether : hexanes), afforded the title compound as a colorless oil, 86% isolated.

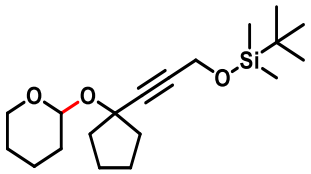
TLC: R_f = 0.51 (10% ether : hexanes), UV, I_2, vanillin stain (blue spot)

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.07 (dd, *J* = 5.2, 1.2 Hz, 1H), 4.36 (s, 2H), 3.96-3.90 (m, 1H), 3.49-3.44 (m, 1H), 2.00-1.97 (m, 1H), 1.85-1.80 (m, 2H), 1.72-1.56 (m, 6H), 1.55-1.46 (m, 6H), 1.28-1.20 (m, 1H), 0.89 (s, 1H), 0.11 (s, 6H)

^{13}C NMR: (100 MHz, $CDCl_3$) δ 96.0, 86.2, 84.7, 75.2, 63.8, 51.9, 38.9, 38.5, 32.3, 29.9, 25.6, 25.4, 20.8, 18.4, -4.9

tert-Butyldimethyl((3-(1-((tetrahydro-2*H*-pyran-2-yl)oxy)cyclopentyl)prop-2-yn-1-yl)oxy)silane

Notebook: DJL-2-129, DJL-4-209



Purification: column chromatography on silica gel eluting with 2% then 5% (ether : hexanes), colorless oil, 89%.

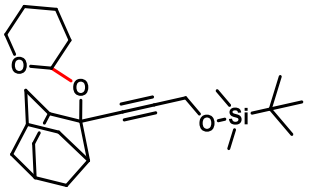
TLC: R_f = 0.55 (10% ether : hexanes), UV, I_2, vanillin stain (blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.04 (dd, *J* = 5.6, 3.2 Hz, 1H), 4.35 (s, 2H), 3.94-3.89 (m, 1H), 3.53-3.47 (m, 1H), 2.24-2.18 (m, 1H), 2.00-1.47 (m, 13H), 0.91 (s, 9H), 0.12 (s, 6H)

^{13}C NMR: (125 MHz, $CDCl_3$) δ 96.7, 86.6, 83.3, 81.0, 63.6, 52.0, 41.4, 40.0, 32.1, 25.9, 25.6, 23.4, 23.0, 20.5, 18.4, - 4.9

***tert*-Butyldimethyl((3-((1*S*,2*R*,5*R*)-2-((tetrahydro-2*H*-pyran-2-yl)oxy)adamantan-2-yl)prop-2-yn-1-yl)oxy)silane**

Notebook: DJL-4-189



Purification: column chromatography on silica gel eluting with pentanes, then 2% (ether : hexanes), highly viscous oil, 81%.

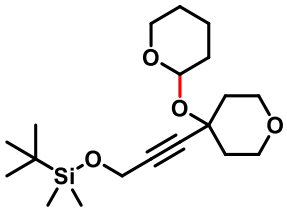
TLC: R_f = 0.25 (2% ether : hexanes), UV, I_2, vanillin stain (merlot spot)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.18 – 5.06 (m, 1H), 4.39 (s, 2H), 3.98 (m, 1H), 3.55 – 3.45 (m, 1H), 2.29 (m, 1H), 2.22 – 2.07 (m, 4H), 1.93 (s, 1H), 1.86 (m, 1H), 1.80 – 1.67 (m, 7H), 1.54 (m, 6H), 0.93 – 0.90 (m, 9H), 0.20 – 0.03 (m, 6H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 96.2, 86.6, 85.5, 78.9, 64.1, 51.9, 38.1, 38.1, 37.1, 35.6, 35.3, 32.5, 32.1, 32.0, 31.7, 27.2, 26.9, 25.9, 25.6, 20.7, -4.9, -4.9.

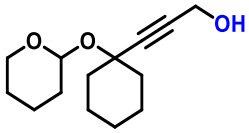
***tert*-Butyldimethyl((3-(4-((tetrahydro-2*H*-pyran-2-yl)oxy)tetrahydro-2*H*-pyran-4-yl)prop-2-yn-1-yl)oxy)silane**

Notebook: DJL-5-297-step-I



Compound directly used crude in subsequent TBAF protection step (see below for analysis of the deprotected molecule).

3-(1-((Tetrahydro-2*H*-pyran-2-yl)oxy)cyclohexyl)prop-2-yn-1-ol



To a RBF charged with a magnetic stir bar and dry THF, ~[0.50 M], was added the TBS-protected alcohol and the resulting mixture was brought to 0 ^{o}C, *via* ice/water bath, with stirring (~10-15 min). Once at 0 ^{o}C, solid TBAF•H_2O (1.50 equiv) was added in one portion and the reaction was allowed to warm to rt. Upon TLC analysis (~30-60 min), consumption of starting material was observed, and the reaction was diluted with ether and subsequently transferred to a separatory funnel. The resulting reaction mixture was extracted from DI water with ether (x 3), organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *via* rotary evaporation and loaded onto a silica gel column; elution with 40% (ether : hexanes) afforded the title compound as a colorless oil, 78% isolated.

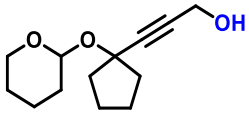
TLC: R_f = 0.37 (40 % EtOAc : hexanes), UV, I_2, vanillin stain (deep purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.12 (dt, *J* = 9.2, 4.5 Hz, 1H), 4.33 (dd, *J* = 23.4, 5.1 Hz, 2H), 3.99 – 3.90 (m, 1H), 3.49 (m, 1H), 2.23 (m, 1H), 2.07 – 1.90 (m, 2H), 1.89 – 1.78 (m, 2H), 1.74 – 1.45 (m, 13H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 99.2, 95.5, 74.8, 63.3, 60.5, 51.2, 38.7, 38.7, 32.2, 32.2, 25.6, 25.4, 23.2, 23.2, 21.2, 20.4, 20.2, 14.3

3-(1-((Tetrahydro-2*H*-pyran-2-yl)oxy)cyclopentyl)prop-2-yn-1-ol

Notebook: DJL-2-134, DJL-4-210



Purification: column chromatography on silica gel eluting with 40% (ether : hexanes) then 100% ether, colorless oil, 88%.

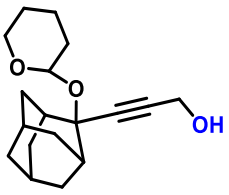
TLC: R_f = 0.17 (30% ether : hexanes), UV, I_2, vanillin stain (deep purple spot)

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.05 (dd, *J* = 4.8, 3.2 Hz, 1H), 4.28 (d, *J* = 6.4 Hz, 2H), 3.95-3.89 (m, 1H), 3.54-3.49 (m, 1H), 2.37-2.30 (m, 1H), 2.22-2.15 (m, 1H), 2.01-1.88 (m, 2H), 1.85-1.75 (m, 4H), 1.74-1.64 (m, 3H), 1.58-1.48 (m, 4H)

^{13}C NMR: (100 MHz, $CDCl_3$) δ 96.3, 87.4, 83.0, 80.7, 63.3, 51.2, 41.2, 40.3, 32.0, 25.5, 23.4, 23.0, 20.1

3-((1*S*,2*R*,5*R*)-2-((Tetrahydro-2*H*-pyran-2-yl)oxy)adamantan-2-yl)prop-2-yn-1-ol

Notebook: DJL-4-191



Purification: column chromatography on silica gel eluting with 50% (ether : hexanes), white solid, 89%.

TLC: R_f = 0.11 (20% ether : hexanes), UV, I_2, vanillin stain (velvet spot)

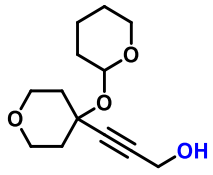
R_f = 0.21 (40% ether : hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.18 (m, 1H), 4.30 (s, 2H), 3.99 (m, 1H), 3.53 (m, 1H), 2.60-2.30 (bs, 1H), 2.27 (m, 1H), 2.19-2.04 (m, 4H), 1.94 (s, 1H), 1.82-1.67 (m, 8H), 1.63-1.49 (m, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 95.3, 78.5, 66.0, 63.4, 63.4, 51.2, 38.0, 37.7, 37.5, 35.6, 35.5, 35.4, 32.4, 32.1, 32.0, 31.7, 27.1, 26.9, 25.7, 20.2, 20.2, 15.4

3-(4-((Tetrahydro-2*H*-pyran-2-yl)oxy)tetrahydro-2*H*-pyran-4-yl)prop-2-yn-1-ol

Notebook: DJL-5-297-step-II



Purification: column chromatography on silica gel eluting with 25% then 35% (ether : DCM), clear colorless oil, 33% (over 2 steps).

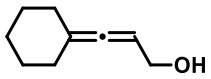
TLC: UV, I_2, vanillin stain (blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) 5.17 (t, *J* = 3.6 Hz, 1H), 4.30 (d, *J* = 5.7 Hz, 2H), 3.92 (m, 1H), 3.86 (m, 2H), 3.71 – 3.65 (m, 1H), 3.61 (m, 1H), 3.54 – 3.48 (m, 1H), 2.83 – 2.19 (m, 1H), 2.01 – 1.90 (m, 2H), 1.89 – 1.81 (m, 3H), 1.74 – 1.66 (m, 1H), 1.57 – 1.48 (m, 4H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 95.5, 85.4, 72.0, 66.0, 64.8, 63.1, 50.9, 39.0, 38.9, 31.9, 25.5, 20.0, 15.3

3-Cyclohexylideneprop-2-en-1-ol

Notebook: DJL-3-277, DJL-4-092/140/225, DJL-5-051/188, DJL-6-014



To a dry RBF charged with a stir bar was added LAH (lithium aluminum hydride), the flask was subsequently diluted with dry ether, ~[0.25 M], and brought to 0 ^{o}C. Then, a solution of the propargyl –OTHP alcohol in dry ether, ~[1.0 M], was added dropwise to this solution with 18G vent needles and a strong flow of argon. TLC analysis (see below) after ~2 h usually indicates a complete reaction. The rubber septum was removed from the RBF and an air condenser was attached. Still at 0 ^{o}C, the reaction was diluted with more ether and **slowly** was added dropwise (over ~20-45 min depending on scale) 15 mL of saturated aqueous Na_2SO_4. Once the salts precipitated at the bottom of the RBF had turned from grey to white and hydrogen evolution had ceased, then DI water was added to help homogenize the resulting mixture (this greatly simplifies aqueous workup). Transfer of this mixture to a separatory funnel with ether and water followed by extraction with ether (x 3), drying of the organic extracts over anhydrous Na_2SO_4, filtration, and concentration *via* rotary evaporation provided the crude material which was purified *via* silica gel chromatography eluting with 40% then 50 % (ether : hexanes), to afford the title compound as a colorless oil, 69 - 81%.

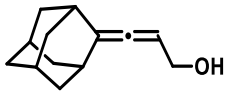
TLC: R_f = 0.26 (40% ether : hexanes), UV, I_2, vanillin stain (light grey spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.31 – 5.03 (m, 1H), 4.06 (t, J = 5.5 Hz, 2H), 2.15 – 2.10 (m, 4H), 1.63 – 1.56 (m, 4H), 1.55 – 1.49 (m, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 197.2, 106.0, 89.8, 61.3, 31.6, 27.6, 26.1

3-((1*R*,3*R*,5*R*,7*R*)-Adamantan-2-ylidene)prop-2-en-1-ol

Notebook: DJL-4-193



Purification: column chromatography on silica gel eluting with 40% then 50% (ether : hexanes), white crystalline solid, 27%.

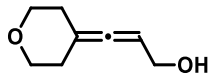
TLC: R_f = 0.36 (40% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.24 (td, *J* = 5.5, 2.0 Hz, 1H), 4.07 (d, *J* = 5.5 Hz, 2H), 2.51 (s, 2H), 1.97 (s, 2H), 1.93 – 1.85 (m, 8H), 1.81 (s, 2H), 1.60 – 1.42 (m, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 193.1, 114.0, 90.7, 61.5, 39.4, 38.6, 37.1, 35.2, 28.2, 28.1

3-(Tetrahydro-4*H*-pyran-4-ylidene)prop-2-en-1-ol

Notebook: DJL-6-002/070

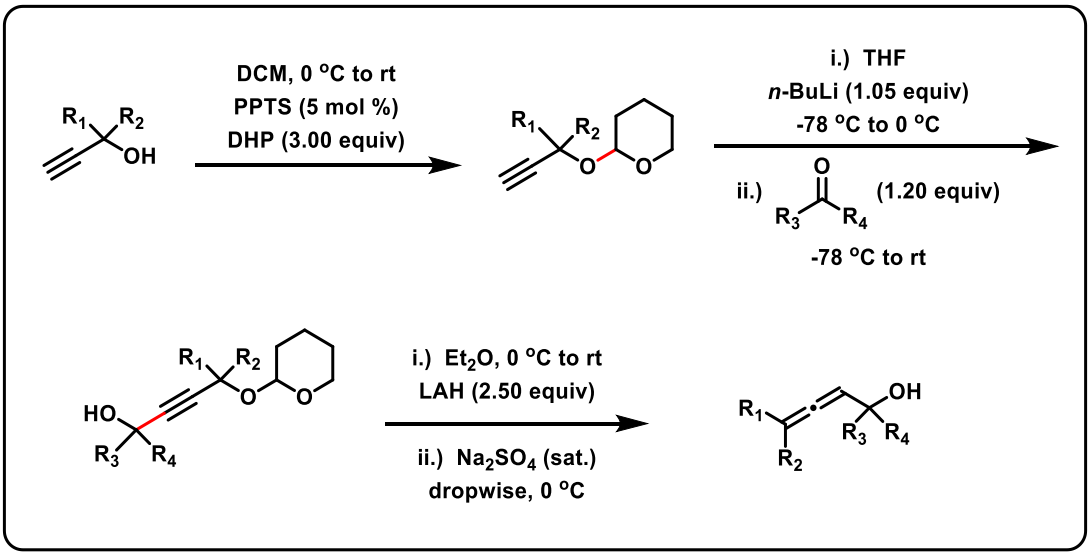


Purification: column chromatography on silica gel eluting with 20% then 30% (ether : DCM), white crystalline solid, 46%

TLC: R_f = 0.23 (25% ether : DCM), UV, I_2

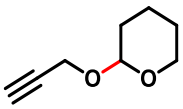
^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.41 – 5.17 (m, 1H), 4.11 (d, *J* = 5.0 Hz, 2H), 3.75 – 3.69 (m, 4H), 2.30 – 2.22 (m, 4H)

Route 2: [3]



2-(Prop-2-yn-1-yloxy)tetrahydro-2H-pyran

Notebook: DJL-3-262, DJL-4-008/050/061/164/299, DJL-5-086/118



To a RBF charged with a magnetic stir bar and dry DCM, ~ [0.50 M], was added the alcohol and the resulting solution was brought to 0°C with stirring. At 0 °C, catalytic PPTS (pyridinium *p*-toluene sulfonate, ~ 2-3 mol %) was added in one portion and the mixture was stirred for ~10-15 min. Then, DHP (1.50 – 2.00 equiv) was introduced dropwise and the reaction was allowed to warm to rt overnight. Once the reaction was complete *via* TLC analysis (see below) the reaction was diluted with DCM and quenched with K_2CO_3. The resulting mixture was then passed through a plug of Celite / sand / Celite / sand (the extra layers of sand helps to gather un-wanted salts and DHP promoted polymeric material). After concentration *via* rotary evaporation the resulting crude oil was loaded onto a silica column

with minimal amounts of hexanes to assure quantitative transfer. The product was purified *via* column chromatography on silica gel, eluting with hexanes followed by 2% (ether : hexanes), to obtain the title compound as a colorless oil, 70-93%.

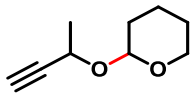
TLC: R_f = 0.33 (10% ether : hexanes), UV, I_2, vanillin stain (purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.81 (bt, 1H), 4.25 (qdd, *J* = 15.7, 2.4, 1.7 Hz, 2H), 3.86 – 3.79 (m, 1H), 3.53 (m, 1H), 2.40 (td, *J* = 2.4, 0.6 Hz, 1H), 1.87 – 1.77 (m, 1H), 1.76 – 1.69 (m, 1H), 1.65 – 1.50 (m, 4H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 97.0, 79.9, 74.1, 62.1, 54.1, 30.3, 25.4, 19.1

2-(But-3-yn-2-yloxy)tetrahydro-2*H*-pyran

Notebook: DJL-4-165



Purification: column chromatography on silica gel eluting with 2% (ether : hexanes), colorless oil, 70%.

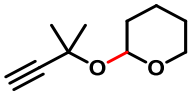
TLC: R_f = 0.33 (10% ether : hexanes), UV, I_2, vanillin stain (purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.96 – 4.72 (m, 1H), 4.60 – 4.40 (m, 1H), 4.02 – 3.75 (m, 1H), 3.59 – 3.43 (m, 1H), 2.48 – 2.30 (m, 1H), 1.88 – 1.65 (m, 2H), 1.66 – 1.48 (m, 4H), 1.49 – 1.34 (m, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 97.3, 96.1, 84.8, 83.8, 72.6, 72.0, 62.7, 62.4, 62.3, 60.7, 30.7, 30.6, 25.6, 25.5, 22.2, 22.0, 19.6, 19.2

2-((2-Methylbut-3-yn-2-yl)oxy)tetrahydro-2*H*-pyran

Notebook: DJL-3-281, DJL-5-169/198



Purification: column chromatography on silica gel eluting with 3% (ether : hexanes), colorless oil, 65%.

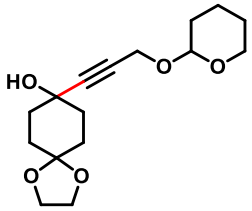
TLC: R_f = 0.49 (20% ether : hexanes), UV, I_2, vanillin stain (purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.12 – 4.96 (m, 1H), 3.97 – 3.91 (m, 1H), 3.53 – 3.45 (m, 1H), 2.42 (s, 1H), 1.89 – 1.78 (m, 1H), 1.75 – 1.67 (m, 1H), 1.60 – 1.44 (m, 10H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 96.3, 86.5, 72.0, 71.0, 63.4, 32.1, 30.7, 29.9, 25.5, 20.6

8-(3-((Tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)-1,4-dioxaspiro[4.5]decan-8-ol

Notebook: DJL-4-175, DJL-5-114



To a RBF charged with a magnetic stir bar and dry THF, ~ [0.25 M], was added the alkyne and the resulting solution was brought to -78 ^{o}C with stirring. Once at -78 ^{o}C, *n*-BuLi (~[2.25 M] in hexanes) (1.05 equiv) was added dropwise, and the mixture was then stirred for ~ 30-45 min at -78 ^{o}C and then ~ 30 min at rt. After that time the solution was again brought to -78 ^{o}C and a solution, ~ [1.0 M], of the desired ketone in dry THF was added dropwise and allowed to stir overnight (~ 8-12 h). Once the reaction was complete *via* TLC analysis (see below) the reaction was quenched with saturated aqueous ammonium chloride, followed by

transfer to a separatory funnel containing DI water and diethyl ether. Extraction with ether (x 3) followed by drying of the organic layers with anhydrous Na_2SO_4, salt filtration and subsequent concentration *via* rotary evaporation provided the crude material which was then subjected to column chromatography on silica gel, eluting with 50% then 75%% (EtOAc : hexanes), to obtain the title compound as a clear colorless oil, 65-95% isolated.

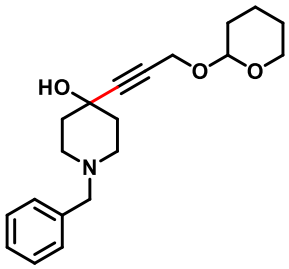
TLC: R_f = 0.21 (50% EtOAc : hexanes), UV, I_2, vanillin stain (merlot spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.80 (dt, *J* = 6.6, 3.3 Hz, 1H), 4.33 – 4.22 (m, 2H), 3.93 (m, 4H), 3.86 – 3.77 (m, 1H), 3.59 – 3.43 (m, 1H), 2.46 – 2.11 (m, 1H), 1.97 – 1.86 (m, 4H), 1.83 – 1.69 (m, 6H), 1.63 – 1.49 (m, 4H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 108.1, 96.9, 64.4, 64.4, 62.1, 60.5, 54.4, 37.2, 31.4, 30.4, 25.5, 21.2, 19.1, 14.3

1-Benzyl-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)piperidin-4-ol

Notebook: DJL-4-224, DJL-5-095



Purification: column chromatography on silica gel eluting with 60% then 80% (ether : DCM), then 40% (acetone : hexanes), light yellow oil, 85%.

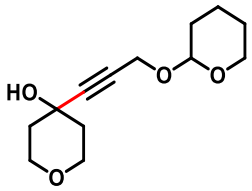
TLC: R_f = 0.35 (80% ether : DCM), UV, I_2, vanillin stain (purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 4H), 7.26 – 7.20 (m, 1H), 4.86 – 4.77 (m, 1H), 4.38 – 4.24 (m, 2H), 3.90 – 3.78 (m, 1H), 3.57 – 3.50 (m, 3H), 2.61 (m, 2H), 2.41 – 2.32 (m, 2H), 1.98 – 1.89 (m, 2H), 1.87 – 1.69 (m, 4H), 1.65 – 1.52 (m, 4H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 138.7, 129.3, 129.2, 128.3, 128.3, 127.1, 96.8, 66.0, 62.9, 62.1, 54.3, 49.6, 39.3, 37.1, 30.4, 25.5, 19.2, 15.4

4-(3-((Tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)tetrahydro-2*H*-pyran-4-ol

Notebook: DJL-5-127/199



Purification: column chromatography on silica gel eluting with 20% then 30% (ether : DCM), colorless oil, 82%.

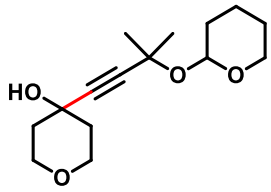
TLC: R_f = 0.27 (40% ether : DCM), UV, I_2, vanillin stain (purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.80 (t, *J* = 3.2 Hz, 1H), 4.37 – 4.24 (m, 2H), 3.91 – 3.80 (m, 3H), 3.68 – 3.59 (m, 2H), 3.57 – 3.50 (m, 1H), 3.18 – 2.04 (m, 1H), 1.97 – 1.88 (m, 2H), 1.77 (m, 4H), 1.64 – 1.50 (m, 4H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 96.9, 88.4, 81.0, 64.9, 64.0, 62.1, 54.3, 40.0, 37.7, 30.4, 25.5, 19.1

4-(3-Methyl-3-((tetrahydro-2*H*-pyran-2-yl)oxy)but-1-yn-1-yl)tetrahydro-2*H*-pyran-4-ol

Notebook: DJL-5-173/202



Purification: column chromatography on silica gel eluting with 20% then 40% (ether : DCM), colorless oil, 65%.

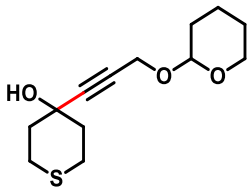
TLC: R_f = 0.29 (40% ether : DCM), UV, I_2, vanillin stain (deep purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.02 (m, 1H), 3.91 (m, 2H), 3.70 (m, 3H), 3.51 – 3.43 (m, 1H), 3.13 – 2.56 (bs, 1H), 1.95 – 1.73 (m, 4H), 1.66 (m, 1H), 1.57 – 1.41 (m, 9H), 1.31 (m, 1H), 1.21 (m, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 96.0, 87.8, 86.5, 70.9, 69.1, 66.0, 65.8, 65.7, 65.1, 64.0, 63.2, 43.2, 40.3, 40.2, 37.7, 32.1, 30.6, 30.3, 25.5, 24.8, 23.3, 20.4, 20.4, 15.4, 14.2

4-(3-((Tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)tetrahydro-2*H*-thiopyran-4-ol

Notebook: DJL-5-115



Purification: column chromatography on silica gel eluting with 40% then 60% (ethyl acetate : hexanes), colorless oil, 93%. Spectra show some unreacted alkyne.

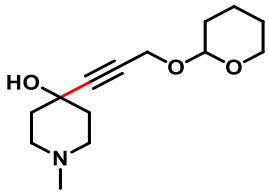
TLC: R_f = 0.36 (50% EtOAc : hexanes), UV, I_2, vanillin stain (velvet spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.78 (m, 1H), 4.35 – 4.22 (m, 2H), 3.81 (ddd, *J* = 11.4, 4.5, 2.2 Hz, 1H), 3.52 (m, 1H), 2.83 – 2.74 (m, 2H), 2.72 – 2.48 (m, 3H), 2.21 – 2.11 (m, 2H), 1.94 – 1.86 (m, 2H), 1.85 – 1.67 (m, 2H), 1.64 – 1.49 (m, 4H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 96.9, 88.3, 81.9, 62.1, 60.5, 54.3, 40.6, 30.3, 26.0, 25.4, 19.1

1-Methyl-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)piperidin-4-ol

Notebook: DJL-5-126/135



Purification: column chromatography on silica gel eluting with 25% then 50% (MeOH : DCM), viscous light yellow oil, 78%.

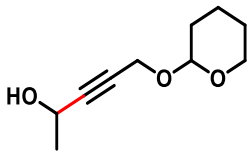
TLC: R_f = 0.26 (20% MeOH : DCM), UV, I_2, vanillin stain (purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.81 (t, *J* = 3.4 Hz, 1H), 4.29 (q, *J* = 15.7 Hz, 2H), 3.89 – 3.76 (m, 1H), 3.56 – 3.48 (m, 1H), 3.40 – 3.14 (bs, 1H), 2.82 – 2.50 (bs, 2H), 2.48 – 2.30 (bs, 2H), 2.27 (s, 3H), 1.97 – 1.89 (m, 2H), 1.88 – 1.69 (m, 4H), 1.65 – 1.48 (m, 4H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 96.7, 89.1, 80.7, 66.0, 62.1, 54.3, 52.4, 46.0, 39.2, 30.4, 25.5, 19.1

5-((Tetrahydro-2*H*-pyran-2-yl)oxy)pent-3-yn-2-ol

Notebook: DJL-4-169



Purification: column chromatography on silica gel eluting with 50% (ethyl acetate : hexanes), colorless oil, 89%.

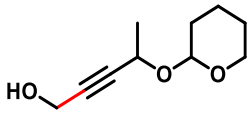
TLC: R_f = 0.13 (30% ethyl acetate : hexanes), UV, I_2, vanillin stain (royal purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.82 – 4.73 (m, 1H), 4.63 – 4.45 (m, 1H), 4.36 – 4.19 (m, 2H), 3.88 – 3.78 (m, 1H), 3.58 – 3.48 (m, 1H), 2.32 – 2.10 (m, 1H), 1.85 – 1.76 (m, 1H), 1.76 – 1.69 (m, 1H), 1.66 – 1.47 (m, 4H), 1.40 (dd, *J* = 35.8, 5.9 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 96.9, 88.1, 80.0, 62.1, 58.4, 54.4, 30.3, 25.5, 24.3, 19.1

4-((Tetrahydro-2*H*-pyran-2-yl)oxy)pent-2-yn-1-ol

Notebook: DJL-4-168



Prepared under slightly different conditions. See lithiation procedure of allenyl benzyl ether **2-(Benzyloxy)buta-2,3-dien-1-ol** shown below.

Purification: column chromatography on silica gel eluting with 40% (EtOAc : hexanes), colorless oil, 93%.

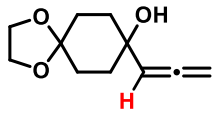
TLC: R_f = 0.47 (50% ether : hexanes), UV, I_2, vanillin stain (violet spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.96 – 4.73 (m, 1H), 4.62 – 4.42 (m, 1H), 4.35 – 4.18 (m, 2H), 4.03 – 3.73 (m, 1H), 3.58 – 3.46 (m, 1H), 1.76 (m, 2H), 1.64 – 1.48 (m, 4H), 1.47 – 1.40 (m, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 96.0, 95.9, 85.5, 83.1, 62.6, 62.6, 60.9, 51.2, 51.1, 30.7, 30.6, 30.6, 25.6, 25.5, 22.2, 19.5, 19.5

8-(Propa-1,2-dien-1-yl)-1,4-dioxaspiro[4.5]decan-8-ol

Notebook: DJL-4-177, DJL-5-116



To a dry RBF charged with a stir bar was added LAH (lithium aluminum hydride, 2.50 equiv), and to the flask was subsequently added dry ether to make a ~[0.25 M] solution, that was cooled to 0 ^{o}C. Then a solution of the propargyl–OTHP alcohol in dry ether, ~[1.0 M], was added dropwise to this solution with 18G vent needles and a strong flow of argon. TLC analysis after ~2 h usually indicates complete conversion. The rubber septum was removed from the RBF and an air condenser was attached. While at 0 ^{o}C the reaction was diluted with more ether to which was **slowly** added dropwise (over ~20-45 min depending on scale), 15 mL of saturated aqueous Na_2SO_4. Once the salts precipitated had turned from grey to white and hydrogen evolution had ceased, then DI water was added to help homogenize the resulting mixture (this greatly simplifies aqueous workup). Transfer of this mixture to a separatory funnel containing ether and water followed by extraction with ether (x 3), drying of the organic extracts over anhydrous Na_2SO_4, filtration and concentration *via* rotary evaporation provided the crude material which was purified *via* silica gel chromatography eluting with 40% then 50% (EtOAc : hexanes), to afford the title compound as a colorless oil, 66%.

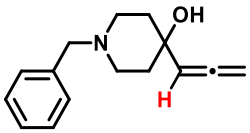
TLC: R_f = 0.34 (50% EtOAc : hexanes), UV, I_2, vanillin stain (Forrest green spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.30 (t, *J* = 6.8 Hz, 1H), 4.93 – 4.86 (d, *J* = 6.5 Hz, 2H), 3.97 – 3.91 (m, 4H), 1.90 (m, 2H), 1.85 – 1.73 (m, 4H), 1.62 (m, 2H), 1.59 – 1.48 (bs, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 206.1, 108.6, 99.1, 78.7, 69.5, 64.4, 64.4, 35.8, 31.0

1-Benzyl-4-(propa-1,2-dien-1-yl)piperidin-4-ol

Notebook: DJL-4-228, DJL-5-104



Purification: column chromatography on silica gel eluting with 100% ether, viscous yellow/ orange oil, 83%.

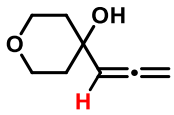
TLC: R_f = 0.34 (100% ether), UV, I_2, vanillin stain (golden yellow spot)

^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 4H), 7.24 (m, 1H), 5.29 (t, *J* = 5.8 Hz, 1H), 4.89 (d, *J* = 5.5 Hz, 2H), 3.52 (d, *J* = 2.0 Hz, 2H), 2.66 – 2.40 (m, 4H), 1.93 – 1.77 (m, 2H), 1.73 – 1.57 (m, 3H)

^{13}C NMR: (151 MHz, $CDCl_3$) δ 197.6, 138.7, 129.2, 128.3, 127.1, 99.3, 78.7, 63.2, 49.8, 37.9, 37.1

4-(Propa-1,2-dien-1-yl)tetrahydro-2*H*-pyran-4-ol

Notebook: DJL-5-129/201



Purification: column chromatography on silica gel eluting with 30% then 40% (ether : DCM), viscous clear colorless oil, 63-84%.

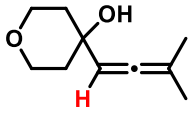
TLC: R_f = 0.34 (40% ether : DCM), UV, I_2, vanillin stain (lavender spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.32 – 5.23 (m, 1H), 4.91 (dd, *J* = 7.0, 1.5 Hz, 2H), 3.83 – 3.77 (m, 2H), 3.69 – 3.64 (m, 2H), 1.93 (bs, 1H), 1.81 (m, 2H), 1.65 – 1.60 (m, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 206.4, 98.9, 78.9, 67.9, 64.3, 38.4

4-(3-Methylbuta-1,2-dien-1-yl)tetrahydro-2*H*-pyran-4-ol

Notebook: DJL-5-175/205



Purification: column chromatography on silica gel eluting with 40% then 60% (ether : hexanes), colorless oil, 50 - 69%.

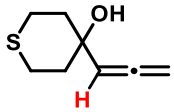
TLC: R_f = 0.26 (60% ether : hexanes), UV, I_2, vanillin stain (deep purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.19 – 4.93 (m, 1H), 3.80 (m, 2H), 3.68 – 3.60 (m, 2H), 1.91 – 1.66 (m, 9H), 1.64 – 1.56 (m, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 199.5, 99.9, 97.7, 68.5, 64.5, 38.6, 20.7

4-(Propa-1,2-dien-1-yl)tetrahydro-2*H*-thiopyran-4-ol

Notebook: DJL-5-117



Purification: column chromatography on silica gel eluting with 40% (ether : hexanes), colorless oil, 66%.

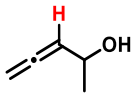
TLC: R_f = 0.28 (40% ether : hexanes), UV, I_2, vanillin stain (merlot spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.30 – 5.19 (m, 1H), 4.92 – 4.89 (m, 2H), 2.93 (ddd, J = 13.5, 9.6, 3.9 Hz, 2H), 2.48 (dt, J = 13.6, 4.6 Hz, 2H), 1.94 – 1.85 (m, 4H), 1.63 (bs, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 206.2, 99.6, 79.1, 68.9, 39.1, 24.7

Penta-3,4-dien-2-ol

Notebook: DJL-4-172



Purification: column chromatography on silica gel eluting with 40% (ether : hexanes), colorless oil.

*Note: The product was not isolated neat after purification (solution in ether) due to its low molecular weight. Thus, it was directly subjected to protection (see below) after NMR analysis (which confirmed the presence of the allene).

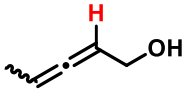
TLC: R_f = 0.31 (40% ether : hexanes), UV, I_2, vanillin stain (pacific blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.35 – 5.21 (q, *J* = 6.3, 1H), 4.89 – 4.82 (m, 2H), 4.42 – 4.31 (m, 1H), 1.31 – 1.30 (m, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 206.8, 96.2, 77.8, 66.0, 14.2

Penta-2,3-dien-1-ol

Notebook: DJL-4-173



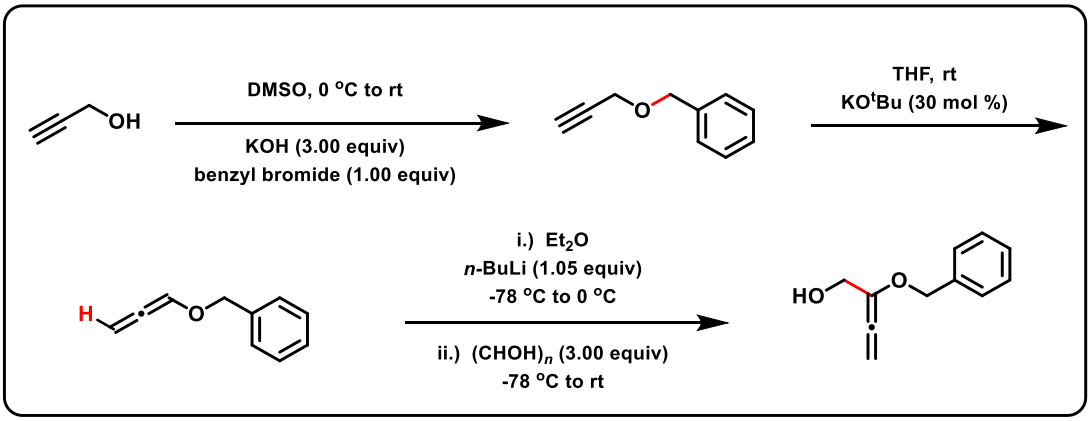
Purification: column chromatography on silica gel eluting with 35% then 40% (ether : hexanes), clear colorless oil, 64 - 70%.

TLC: R_f = 0.27 (40% ether : hexanes), UV, I_2, vanillin stain (robin's egg blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.33 – 5.18 (m, 2H), 4.09 (d, *J* = 3.0 Hz, 2H), 1.79 – 1.70 (m, 1H), 1.68 (dd, *J* = 6.5, 3.5 Hz, 3H)

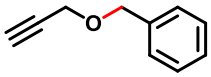
^{13}C NMR: (126 MHz, $CDCl_3$) δ 204.0, 91.3, 88.6, 60.8, 14.4

Route 3: [4]



((Prop-2-yn-1-yloxy)methyl)benzene

Notebook: DJL-4-239/256, DJL-5-006/050/087/130/165/232



A suspension of KOH (3.00 equiv) in DMSO was stirred at rt until all of the KOH pellets had dissolved (if not performed then it becomes very difficult to break up the gelatinous solid). Once dissolved, the mixture was brought to 0 °C and propargyl alcohol (1.00 equiv) was added dropwise, and the solution stirred ~15-20 min followed by dropwise addition of benzyl bromide (1.00 equiv). The resulting solution was allowed to warm with stirring to rt overnight, at which time TLC analysis indicated complete conversion of starting material (see below). The reaction mixture was then diluted with water (keeping the reaction vessel in a water bath to absorb heat from the presence of excess base) and transferred to a separatory funnel with water and ether. The aqueous layer was extracted (x 3) with ether and the combined organic layers were then washed with water (x 4) to help separate residual DMSO from the crude material. Drying of the organic extracts over anhydrous Na_2SO_4, filtration, and

concentration *via* rotary evaporation provided the crude material which was purified *via* silica gel chromatography eluting with pentanes, and then 2% then 10% ether : hexanes, to afford the title compound as a colorless oil, 69 - 81%.

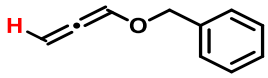
TLC: R_f = 0.38 (2% ether : hexanes), UV, I_2, $KMnO_4$ stain

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 4H), 7.34 – 7.29 (m, 1H), 4.63 (s, 2H), 4.21 – 4.17 (m, 2H), 2.48 (t, J = 2.5 Hz, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 137.4, 128.6, 128.2, 128.0, 79.8, 74.7, 71.7, 57.2

((Propa-1,2-dien-1-yloxy)methyl)benzene

Notebook: DJL-4-241/261/277, DJL-5-011/106/168/179/239



To a solution of potassium *t*-butoxide in THF, ~[0.10-0.25 M] (dilute enough to assure no loss of material on the wall of the RBF; concentration has no beneficial or adverse effect on the reaction), at rt was added 'neat' propargyl benzyl ether. The resulting mixture was then covered with aluminum foil and allowed to stir overnight (~10-12 h; reaction is usually complete within a few hours; however excess stirring has no negative impact upon reaction outcome). Upon TLC analysis, which indicated full conversion (see below), the reaction mixture was diluted with ether and stirred until homogeneous. The resulting mixture was then passed through a plug of Celite / sand / Celite / sand (the extra layers of sand helps to trap KO-*t*-Bu salts). After concentration *via* rotary evaporation the resulting oil should appear light/pale yellow; if coloration is dark orange to red and/or has solid particulates then filtration through a second plug of Celite and sand is performed. The sensitivity of this compound to acidic conditions requires the use of Celite and **not** silica, which will cause product decomposition.

Azeotroping of the pale yellow oil with pentanes and further drying *via* high-vacuum afforded the pure title compound, 90% - quant. Product should be stored shielded from light, under argon at 5 ^{o}C.

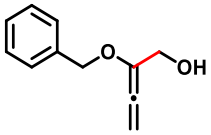
TLC: R_f = 0.50 (2% ether : hexanes), UV, I_2 (strong)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.36 (m, 4H), 7.35 – 7.29 (m, 1H), 6.93 – 6.76 (m, 1H), 5.52 – 5.46 (m, 2H), 4.63 (s, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 201.5, 137.4, 128.5, 128.0, 127.9, 121.8, 91.2, 70.8

2-(Benzyloxy)buta-2,3-dien-1-ol

Notebook: DJL-4-242/248, DJL-5-079/146/174/181



To a RBF charged with a magnetic stir bar and dry ether was added allenyl benzyl ether and the resulting solution, ~ [0.25 M], was cooled to -78 ^{o}C with stirring. Once at -78 ^{o}C, *n*-BuLi (~[2.25 M] in hexanes; 1.05 equiv) was added dropwise, this mixture was then stirred for ~ 30-45 min at -78 ^{o}C and then ~ 30 min at rt. After this time, the solution was again brought to -78 ^{o}C and paraformaldehyde (3.00 equiv) was added in one portion, the reaction mixture was covered with aluminum foil and allowed to stir overnight (~ 8-12 h). Once the reaction was complete *via* TLC analysis (see below) the reaction was quenched with saturated aqueous ammonium chloride (or sat. $NaHCO_3$), followed by transfer to a separatory funnel containing water and diethyl ether. Extraction with ether (x 3) followed by drying of the organic extracts with anhydrous Na_2SO_4, filtration, and subsequent concentration *via* rotary evaporation provided the crude material which was then subjected to column chromatography on silica gel

(*__Note__), eluting with 30% (ether : hexanes), to obtain the title compound as a clear colorless oil or as a light pale yellow oil, 29 - 52% isolated.

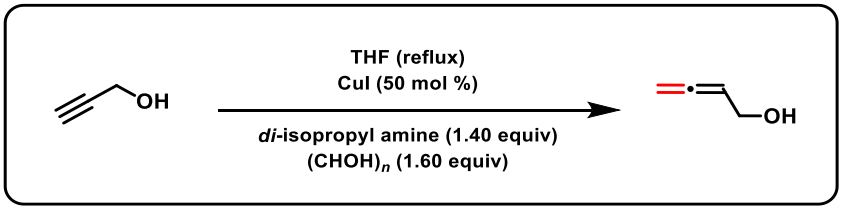
***Note:** The flash column should be packed and run with 1-2% Et_3N to avoid acid mediated decomposition of the cumulated enol ether.

TLC: R_f = 0.28 (40% ether : hexanes), UV, I_2, $KMnO_4$ stain

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 4H), 7.33 – 7.26 (m, 1H), 5.53 (t, *J* = 2.0 Hz, 2H), 4.66 (s, 2H), 4.23 (s, 2H), 2.23 – 1.62 (bs, 1H)

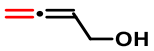
^{13}C NMR: (126 MHz, $CDCl_3$) δ 197.7, 137.3, 132.2, 128.5, 128.1, 128.0, 91.8, 71.0, 62.4

Route 4: [5]



Buta-2,3-dien-1-ol

Notebook: DJL-4-011/017/042, DJL-5-072



To a RBF equipped with a stir bar was sequentially added CuI (50 mol %), paraformaldehyde (1.60 equiv) and dry THF (~[0.50 M]). This mixture was stirred at rt during the subsequent, dropwise addition of diisopropylamine (1.40 equiv) followed by propargyl alcohol (1.00 equiv). A water-jacketed reflux condenser was then attached to the RBF and the reaction mixture was transferred to an oil bath and brought to reflux (oil bath set to 85 ^{o}C), and

allowed to stir overnight (no significant precautions were taken to exclude moisture for the reaction mixture once at reflux).

After being heated for ~20-24 h the reaction was allowed to cool to rt and the resulting deep red/ brown solution was concentrated to ~1/4 its volume *via* rotary evaporation (**with the water bath at, or below, rt**) and subsequently diluted with ether and passed through a short plug of silica gel / Celite / sand (for a large scale reaction this process is performed twice). The crude ethereal solution was then transferred to an Erlenmeyer flask containing a strong stir bar and diluted with an equal volume of saturated aqueous NaCl. Concentrated HCl, ~[12 N], was periodically added dropwise with stirring until the acidity of the mixture had reached pH~2-3. After stirring for another ~10-15 min the contents of the flask were passed through a tall suction column of sand / Celite / sand / Celite / sand, eluting with ether (this is to filter off much of the produced salts from the crude reaction mixture). Transfer of both the aqueous and organic phases to a separatory funnel and extraction *via* ether washes (x 3-4), drying of the organic layer with anhydrous Na_2SO_4/$MgSO_4$, salt filtration and careful concentration *via* rotary evaporation (with the water bath at, or below, rt) afforded the crude product as a light orange to yellow oil.

Kugelrohr (bulb-to-bulb) distillation, first at rt with a vacuum pressure set to 30 Torr (throughout), separated unreacted propargyl alcohol from the crude mixture (light yellow oil). After which a clean ‘glass bulb’ was attached and the Kugelrohr apparatus was slowly heated to 40 ^{o}C. If any more material was distilled at this point it was set aside and checked separately for the presence of trace propargyl alcohol. Once no additional distillate condensed at 40 ^{o}C, another clean ‘glass bulb’ was inserted and the temperature was slowly raised to 52-53 ^{o}C.

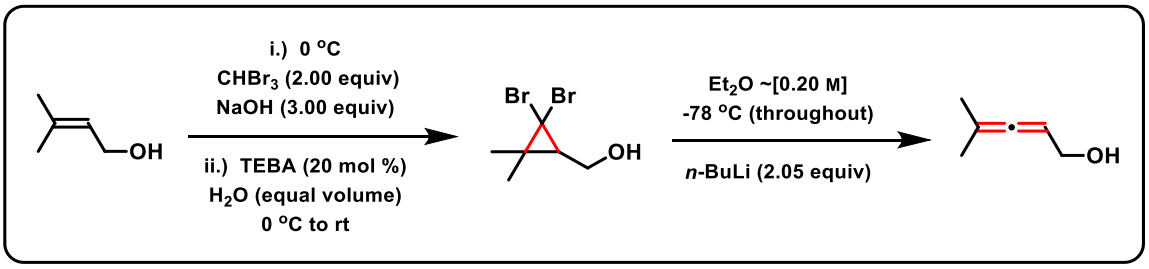
Bulb-to-bulb collection of the clear colorless distillate at this pressure and temperature was confirmed to be the desired title product, 11–22% isolated.

TLC: R_f = 0.15 (40% ether : hexanes), UV, I_2 (strong), $KMnO_4$

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.44 – 5.17 (pent, J = 6.4 Hz, 1H), 4.89 – 4.79 (m, 2H), 4.12 (M, 2H), 2.10 – 1.95 (m, 1H)

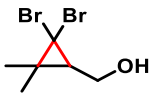
^{13}C NMR: (126 MHz, $CDCl_3$) δ 208.0, 91.0, 76.9, 60.3

Route 5: [6]



(2,2-Dibromo-3,3-dimethylcyclopropyl)methanol

Notebook: DJL-3-042/048/052/057/070/077/196/211



To a RBF charged with a 'strong' magnetic stir bar was sequentially added but-2-en-1-ol (1.00 equiv), bromoform (2.00 equiv), DI water leading to a mixture, ~[0.50 M], and 20 mol % TEBA (triethylbenzylammonium chloride) and the resulting mixture was brought to 0 °C, with stirring, with an ice/water bath (reaction **not** performed under argon). Once the mixture was cooled, NaOH pellets (3.00 equiv) were added in one portion and an exothermic reaction occurred. ***Note:** Periodic venting of the 'septum-sealed' reaction vessel with an 18G needle is performed every ~5-10 min during the initial hour of the reaction. After stirring

overnight at rt, the reaction was diluted with DI water and transferred to a separatory funnel with DCM washes. Addition of aqueous NaCl (sat.) and extraction of the aqueous layer with DCM (x 3), drying of the collected organic layers with anhydrous $MgSO_4$, salt filtration, and concentration *via* rotary evaporation provided the deep orange colored crude residue. Column chromatography on silica gel eluting with pentanes followed by 20% (EtOAc : hexanes) afforded the title compound as a viscous light yellow-orange oil which crystallizes upon storage at 5 ^oC; 36–65% isolated.

***Note:** Use of initial column volumes (CV's) of pentane helps to separate the desired product from unreacted bromoform, which inevitably streaks throughout the column if not passed through with non-polar solvent first.

TLC: Product R_f = 0.30, (25% EtOAc : hexanes), UV (only), I_2

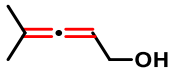
Starting material R_f = 0.27, (25% EtOAc : hexanes), UV, I_2 (only)

^1H NMR: (500 MHz, $CDCl_3$) δ 3.75 (d, *J* = 7.0 Hz, 2H), 1.75 (t, *J* = 7.3 Hz, 1H), 1.65 – 1.54 (m, 1H), 1.42 (s, 3H), 1.27 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 62.2, 44.6, 40.7, 29.2, 27.5, 19.6

4-Methylpenta-2,3-dien-1-ol

Notebook: DJL-3-050/055/060/067/074/191/201/213/226, DJL-4-147



To a RBF under a positive flow of argon and charged with a magnetic stir bar and dry ether, ~[0.10 M], was added (2,2-dibromo-3,3-dimethylcyclopropyl)methanol and the resulting mixture was covered with aluminum foil and brought to -78 ^oC *via* a dry ice/acetone bath. Once at -78 ^oC, *n*-BuLi (~[2.25 M] in hexanes; 2.05 equiv) was added dropwise. Upon complete

addition of base the reaction was stirred for ~5-10 min and analyzed *via* TLC (which usually indicates full consumption of starting material), and the reaction was immediately quenched with saturated aqueous NH_4Cl (extended reaction times result in an increase of by-product formation). Transfer to a separatory funnel and extraction with ether (x 3), drying over anhydrous Na_2SO_4, salt filtration, and rotary evaporation (at or below rt and only to the point of ~1/8 the reaction volume), provided the crude oil. Purification *via* column chromatography on silica gel eluting with pentanes and then 20% then 30% (ether : hexanes) afforded the title compound as a colorless oil which was only concentrated to ~1/10 its volume and used as such in the subsequent protection step (for yield over 2 steps see below).

TLC: Product R_f = 0.21, (25% ether : hexanes), UV, I_2 (only)

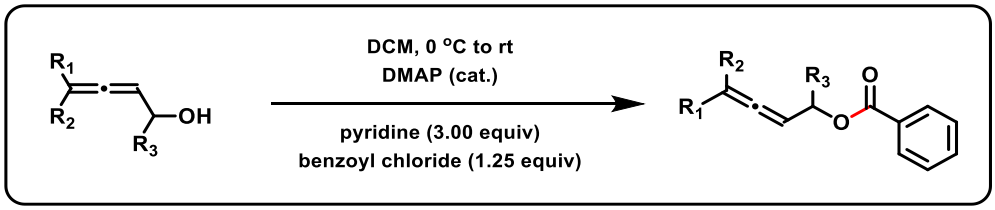
Starting material R_f = 0.17, (25% ether : hexanes), UV (only), I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.18 (m, 1H), 4.06 (t, *J* = 5.5 Hz, 2H), 1.71 (d, *J* = 2.5 Hz, 6H), 1.52 (bs, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 200.7, 98.6, 90.0, 61.1, 20.7

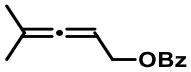
1.2 Protection of allenols

Method 1: Primary and secondary allenols



4-Methylpenta-2,3-dien-1-yl benzoate

Notebook: DJL-3-056/069/125/193/202/227



To an oven dried RBF charged with a stir bar and dry DCM, ~[0.25 M], was added the allenyl alcohol and the mixture was cooled to 0 °C *via* an ice/water bath. Once at 0 °C, a few crystals of DMAP (dimethylaminopyridine) were added, followed by the dropwise addition of dry pyridine (3.00 equiv). After this mixture was stirred for ~10-15 min, benzoyl chloride (1.25 equiv) was added dropwise and the resulting solution was stirred with warming to rt (anywhere from 2-20 h, usually compete within 1-2 h, however, prolonged stirring has no adverse effect on the reaction). Once TLC analysis indicated full consumption of starting material (see below) the stir bar was removed from the reaction and the solution was directly concentrated *via* rotary evaporation until salt formation began to occur. At this time the crude RBF was diluted with pentanes and pre-dried silica gel (***Note**) was added to the RBF followed by re-subjection to concentration (try to avoid bumping). If the initial attempt to obtain a 'dry-loaded' crude mixture results in a 'chunky' collection of silica and salt, then a little more dried silica was added as well as more pentanes, again followed by concentration *via* rotary evaporation. Once a free-flowing silica-embedded dry load has been achieved, the crude

material was transfer to a packed silica flash column and eluted with pentanes, and then 1% (ether : hexanes) to afford the title compound as a colorless oil, 68%.

***Note:** Pre-drying the silica used for dry-loading by passing ~250 mL of acetone followed by ~250 mL pentanes through a plug of 'stock' silica is necessary for easily isomerizable allenoates. Otherwise, unidentified decomposition will occur upon subjection to column chromatography. Not all allenoates were dry loaded and/or required 'pre-dried' silica gel; however, those that did will be indicated below.

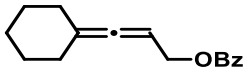
TLC: R_f = 0.48 (10% ether : hexanes), UV, I_2, vanillin stain (blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.14 – 7.96 (m, 2H), 7.59 – 7.52 (m, 1H), 7.46 – 7.41 (m, 2H), 5.33 – 5.12 (m, 1H), 4.77 (d, *J* = 6.5 Hz, 2H), 1.71 (d, *J* = 3.0 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 166.5, 133.0, 130.6, 129.7, 128.4, 97.6, 85.0, 63.8, 20.4

3-Cyclohexylideneallyl benzoate

Notebook: DJL-4-097/142/233, DJL-5-057/189, DJL-6-017



Purification: column chromatography on silica gel eluting with pentanes, then 5% (ether : hexanes), clear colorless oil, 86 - 97%.

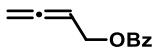
TLC: R_f = 0.59 (20% ether : hexanes), UV, I_2, vanillin stain (grey/blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.22 – 8.03 (m, 2H), 7.59 – 7.52 (m, 1H), 7.43 (m, 2H), 5.42 – 5.05 (m, 1H), 4.78 (d, *J* = 6.5 Hz, 2H), 2.16 – 2.09 (m, 4H), 1.62 – 1.48 (m, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 200.0, 166.5, 133.0, 130.6, 129.8, 128.4, 104.8, 84.9, 64.0, 31.3, 27.3, 26.1

Buta-2,3-dien-1-yl benzoate

Notebook: DJL-4-014/023/048, DJL-5-083



***Note:** Pre-dried silica used for dry loading crude material.

Purification: column chromatography on silica gel eluting with 1 CV pentanes then 3% (ether : hexanes), clear colorless oil, 88%.

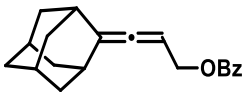
TLC: R_f = 0.57 (20% ether : hexanes), UV, I_2, vanillin stain (light purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.11 – 8.01 (m, 2H), 7.59 – 7.53 (m, 1H), 7.49 – 7.39 (m, 2H), 5.42 (p, *J* = 6.8 Hz, 1H), 4.89 (m, 2H), 4.83 (m, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 209.9, 166.4, 133.1, 130.3, 129.8, 128.5, 86.6, 76.9, 62.8

3-(Adamantan-2-ylidene)allyl benzoate

Notebook: DJL-4-194, DJL-5-035



Purification: column chromatography on silica gel eluting with 1 CV pentanes then 1% (ether : hexanes), highly viscous clear colorless oil, 83 – 94%.

TLC: R_f = 0.61 (20% ether : hexanes), UV, I_2, vanillin stain (violet spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.13 – 8.01 (m, 2H), 7.58 – 7.52 (m, 1H), 7.46 – 7.39 (m, 2H), 5.44 – 5.09 (t, *J* = 6.5 Hz, 1H), 4.79 (d, *J* = 6.5 Hz, 2H), 2.53 (s, 2H), 1.96 – 1.79 (m, 12H)

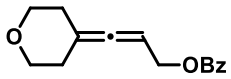
^{13}C NMR: (126 MHz, $CDCl_3$) δ 196.1, 166.5, 133.0, 130.6, 129.8, 128.4, 112.4, 85.5, 64.3, 38.9, 38.6, 37.1, 34.8, 28.1, 28.1

IR: 2908, 2852, 1966, 1719, 1455, 1262 cm^{-1}

HRMS: (EI) calculated for [$C_{20}H_{22}O_2$] : 294.1620 $[M]^{+\bullet}$, found 294.1611

3-(Tetrahydro-4*H*-pyran-4-ylidene)allyl benzoate (33)

Notebook: DJL-6-007/073



Purification: column chromatography on silica gel eluting with 10% then 15% (ether : hexanes), viscous clear colorless oil, 77%.

TLC: R_f = 0.26 (20% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.14 – 7.97 (m, 2H), 7.61 – 7.53 (m, 1H), 7.48 – 7.40 (m, 2H), 5.52 – 5.12 (m, 1H), 4.80 (d, *J* = 6.5 Hz, 2H), 3.73 (m, 2H), 3.62 (m, 2H), 2.29 – 2.19 (m, 4H)

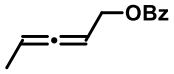
^{13}C NMR: (126 MHz, $CDCl_3$) δ 200.0, 166.4, 133.1, 130.4, 129.7, 128.5, 100.5, 86.5, 68.5, 63.3, 31.3

IR: 2957, 2913, 2852, 1972, 1719, 1455, 1267, 1097 cm^{-1}

HRMS: (EI) calculated for [$C_{15}H_{17}O_3$] : 245.1178 $[M+H]^+$, found 245.1170

Penta-2,3-dien-1-yl benzoate

Notebook: DJL-4-192



***Note:** Pre-dried silica used for dry loading crude material.

Purification: column chromatography on silica gel eluting with 1 CV pentanes then 2% then 5% (ether : hexanes), clear colorless oil, 83%.

TLC: R_f = 0.43 (10% ether : hexanes), UV, I_2, vanillin stain (grey/ blue spot)

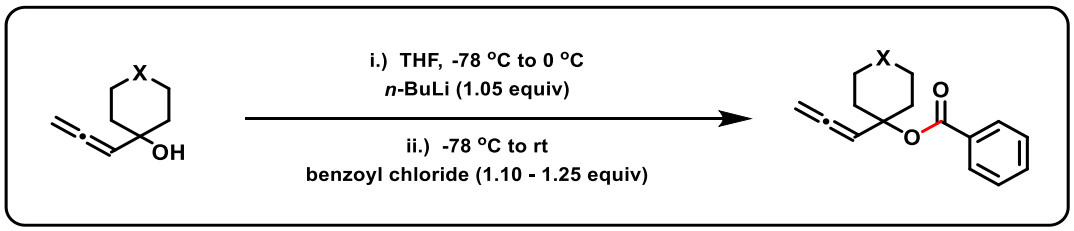
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.17 – 7.95 (m, 2H), 7.62 – 7.51 (m, 1H), 7.48 – 7.36 (m, 2H), 5.50 – 5.30 (m, 1H), 5.30 – 5.11 (m, 1H), 4.82 – 4.77 (m, 2H), 1.75 – 1.64 (m, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 206.4, 166.5, 133.0, 130.5, 129.8, 128.5, 87.9, 86.6, 63.4, 14.1

IR: 2945, 1970, 1721, 1455, 1261 cm^{-1}

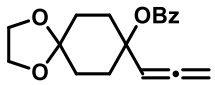
HRMS: (EI) calculated for [$C_{12}H_{12}O_2$] : 188.0837 $[M]^{+\bullet}$, found 188.0829

Method 2: Tertiary allenols



8-(Propa-1,2-dien-1-yl)-1,4-dioxaspiro[4.5]decan-8-yl benzoate

Notebook: DJL-4-215, DJL-5-120



To a RBF charged with a magnetic stir bar and dry THF, ~ [0.25 M], was added the corresponding allenyl alcohol (1.00 equiv) and the resulting solution was brought to -78 °C with stirring. Once at -78 °C, *n*-BuLi (~[2.25 M] in hexanes; 1.05 equiv) was added dropwise, and the mixture was then stirred for ~ 30-45 min at -78 °C and then for ~ 30 min at rt. At that time the solution was again brought to -78 °C and a solution of benzoyl chloride in dry THF, ~[1.0 M], was added dropwise. The reaction was covered with aluminum foil and allowed to stir overnight (~ 8-12 h). Once the reaction was complete *via* TLC analysis (see below) the reaction was quenched with saturated aqueous ammonium chloride (or saturated $NaHCO_3$), followed by transfer to a separatory funnel containing water and diethyl ether. Extraction with

ether (x 3) followed by drying of the organic layers with anhydrous Na_2SO_4, salt filtration, and subsequent concentration *via* rotary evaporation provided the crude material which was then subjected to column chromatography on silica gel, eluting with 20% (ether : hexanes), to obtain the title compound as a viscous colorless oil, 82% isolated.

TLC: R_f = 0.25 (20% ether : hexanes), UV, I_2, vanillin stain (deep blue/ green spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.55 – 7.51 (m, 1H), 7.44 – 7.39 (m, 2H), 5.98 – 5.58 (t, *J* = 6.8 Hz, 1H), 4.92 – 4.87 (d, *J* = 6.5 Hz, 2H), 3.95 (s, 4H), 2.48 (dt, *J* = 14.2, 3.4 Hz, 2H), 2.06 – 1.98 (m, 2H), 1.89 – 1.83 (m, 2H), 1.71 (m, 2H)

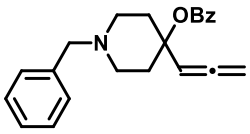
^{13}C NMR: (126 MHz, $CDCl_3$) δ 207.8, 165.5, 132.9, 131.4, 129.6, 128.4, 108.2, 95.0, 80.1, 78.3, 64.5, 64.4, 33.0, 31.0

IR: 2957, 2886, 1955, 1708, 1278, 1240, 1091 cm^{-1}

HRMS: (EI) calculated for $[C_{18}H_{20}O_4]$: 300.1362 $[M]^{+\bullet}$, found 300.1351

1-Benzyl-4-(propa-1,2-dien-1-yl)piperidin-4-yl benzoate

Notebook: DJL-4-232, DJL-5-109



Purification: column chromatography on silica gel eluting with 5% then 10% (ether : DCM), highly viscous light yellow/ orange oil, 70%.

Flash column ran, but not packed, with ~1 – 2 % Et_3N.

TLC: R_f = 0.32 (10% ether : DCM), UV, I_2, vanillin stain (clay/ orange spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.04 – 8.01 (m, 2H), 7.57 (m, 1H), 7.45 (m, 2H), 7.34 – 7.31 (m, 4H), 7.28 – 7.25 (m, 1H), 5.81 (t, *J* = 6.8 Hz, 1H), 4.91 (d, *J* = 6.5 Hz, 2H), 3.52 (s, 2H), 2.69 – 2.58 (m, 2H), 2.49 – 2.37 (m, 4H), 2.06 (m, 2H)

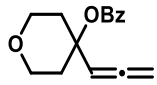
^{13}C NMR: (126 MHz, $CDCl_3$) δ 207.9, 165.3, 138.7, 132.8, 131.6, 129.6, 129.2, 128.4, 128.3, 127.1, 95.2, 79.3, 78.4, 63.2, 49.8, 35.3

IR: 3029, 2935, 2808, 1955, 1713, 1455, 1278 cm^{-1}

HRMS: (EI) calculated for [$C_{22}H_{22}NO_2$] : 332.1651 $[M-H]^+$, found 332.1650

4-(Propa-1,2-dien-1-yl)tetrahydro-2*H*-pyran-4-yl benzoate

Notebook: DJL-5-143/209



Purification: column chromatography on silica gel eluting with 10% then 15% (ether : hexanes), viscous clear colorless oil, 85%.

TLC: R_f = 0.38 (20% ether : hexanes), UV, I_2, vanillin stain (lavender spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.02 (dt, *J* = 8.4, 1.5 Hz, 2H), 7.58 – 7.53 (m, 1H), 7.46 – 7.42 (m, 2H), 5.81 (t, *J* = 6.8 Hz, 1H), 4.96 – 4.93 (d, *J* = 6.5 Hz, 2H), 3.84 – 3.76 (m, 4H), 2.33 (m 2H), 2.09 (m, 2H)

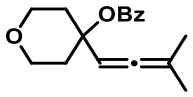
^{13}C NMR: (126 MHz, $CDCl_3$) δ 208.2, 165.3, 133.0, 131.3, 129.6, 128.5, 94.8, 78.7, 78.4, 64.2, 36.0

IR: 2962, 2862, 1954, 1710, 1450, 1278, 1245, 1106 cm^{-1}

HRMS: (EI) calculated for [$C_{15}H_{16}O_3$] : 244.1099 $[M]^{+\bullet}$, found 244.1102

4-(3-Methylbuta-1,2-dien-1-yl)tetrahydro-2*H*-pyran-4-yl benzoate

Notebook: DJL-5-180/210



Purification: column chromatography on silica gel eluting with 10% then 20% (ether : hexanes), viscous clear colorless oil which crystallizes if stored in the freezer (-20°C) to form a white crystalline solid, 74%.

TLC: R_f = 0.52 (40% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 2H), 7.54 (m, 1H), 7.43 (m, 2H), 5.54 (hept, *J* = 2.9 Hz, 1H), 3.83 – 3.74 (m, 4H), 2.32 – 2.27 (m, 2H), 2.09 – 2.03 (m, 2H), 1.71 (d, *J* = 3.0 Hz, 6H)

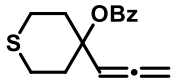
^{13}C NMR: (126 MHz, $CDCl_3$) δ 201.7, 165.3, 132.8, 131.6, 129.5, 128.4, 99.3, 93.3, 79.6, 64.4, 36.2, 20.2

IR: 2957, 2858, 1972, 1713, 1455, 1273, 1102 cm^{-1}

HRMS: (EI) calculated for [$C_{17}H_{20}O_3$] : 272.1412 $[M]^{+\bullet}$, found 272.1404

4-(Propa-1,2-dien-1-yl)tetrahydro-2*H*-thiopyran-4-yl benzoate

Notebook: DJL-5-121



Purification: column chromatography on silica gel eluting with 2% then 10% (ether : hexanes), colorless oil, 34%.

TLC: R_f = 0.56 (20% ether : hexanes), UV, I_2, vanillin stain (crimson spot)

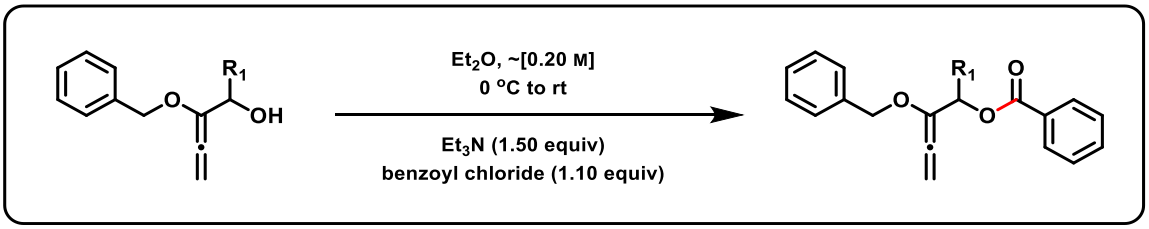
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.03 – 7.97 (m, 2H), 7.56 (m, 1H), 7.46 – 7.42 (m, 2H), 5.75 (t, *J* = 6.8 Hz, 1H), 4.95 – 4.92 (d, *J* = 6.5 Hz, 2H), 2.95 (ddd, *J* = 13.9, 11.4, 2.5 Hz, 2H), 2.74 – 2.69 (m, 2H), 2.59 – 2.54 (m, 2H), 2.07 (ddd, *J* = 14.4, 11.4, 3.4 Hz, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 207.8, 165.1, 133.0, 131.2, 129.6, 128.5, 95.9, 79.5, 78.8, 36.5, 24.4

IR: 2968, 2924, 1955, 1719, 1449, 1432, 1278 cm^{-1}

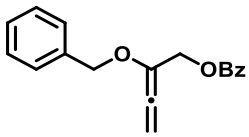
HRMS: (EI) calculated for $[C_{15}H_{16}O_2S]$: 260.0871 $[M]^{+\bullet}$, found 260.0870

Method 3: 2-Benzyloxy allenols



2-(Benzyloxy)buta-2,3-dien-1-yl benzoate

Notebook: DJL-4-250, DJL-5-176/186



To a solution of the allenyl benzyl allenol (1.00 equiv) in dry ether, ~[0.20 M], at 0 °C was added, dropwise, Et_3N (1.50 equiv) and the resulting mixture was stirred for ~5-10 min. Then, 'neat' benzoyl chloride (1.10 equiv) was added dropwise to the reaction vessel; upon compete addition salt formation had already begun. Upon stirring for ~30-45 min (at which point much salt had precipitated from the reaction mixture) TLC analysis indicates complete consumption of starting material (see below). The reaction was then diluted with hexanes and

stirred for ~5-10 min (to aid in further salt precipitation). This mixture was then filtered through a pad of Celite topped with sand and with ether. The resulting crude filtrate was then concentrated *via* rotary evaporation and transferred to a separatory funnel, washed once with saturated aqueous $NaHCO_3$ followed by DI water, dried over anhydrous Na_2SO_4, filtered from salts and, again, concentrated. This yielded the crude material which was purified by flash chromatography on silica gel (***Note**), eluting with pentanes and then 3% (ether : hexanes) to afford the title compound as a colorless oil to a faint yellow oil, 51-79%.

***Note:** The flash column should be packed and ran with 1-2% Et_3N to avoid acid mediated decomposition of the cumulated enol ether.

TLC: R_f = 0.48 (20% ether : hexanes), UV, I_2, vanillin stain (olive green spot)

R_f = 0.39 (10% ether : hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.11 – 8.06 (m, 2H), 7.57 (m, 1H), 7.45 (m, 2H), 7.40 – 7.28 (m, 5H), 5.54 (m, 2H), 4.96 (m, 2H), 4.71 (s, 2H)

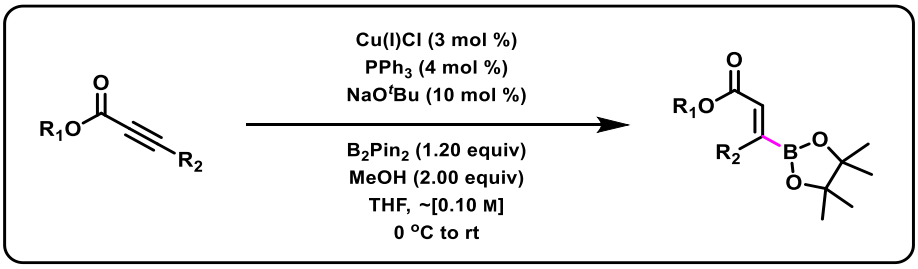
^{13}C NMR: (126 MHz, $CDCl_3$) δ 199.4, 166.3, 137.4, 133.1, 130.2, 129.9, 128.7, 128.5, 128.4, 127.9, 127.8, 91.6, 70.9, 64.0

IR: 3040, 2965, 2924, 1966, 1719, 1455, 1366, 1273 cm^{-1}

HRMS: (EI) calculated for $[C_{18}H_{17}O_3]$: 281.1178 $[M+H]^+$, found 281.1167

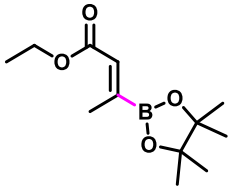
1.3 Synthesis of boron coupling partners

1.3.1 β-Borylated esters [7]



Ethyl (*Z*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate

Notebook: DJL-4-106/240



To a clean and dry RBF was added Cu(I)Cl (3 mol %), triphenylphosphine (4 mol %) and NaO-*t*-Bu (10 mol %) in an argon filled glove box. The sealed RBF was then removed from the glove box and dry THF, ~[0.50 M], was added slowly, washing the walls of the flask to bring all of the salts into solution; this solution was then stirred at rt for ~20 – 30 min. Then the flask was immersed in a rt water bath, followed by the addition of B_2Pin_2 (1.20 equiv) in one portion, subsequent washing of the RBF's walls with minimal THF and continued stirring for ~ 15–20 min. Then the rt water bath was exchanged for a 0 °C ice water bath. At 0 °C, a solution of the ynoate (1.00 equiv) in THF, ~[1.0 M], was added dropwise, followed by dropwise addition of MeOH (2.00 equiv). The resulting reaction mixture was allowed to stir over night, ~12-16 h after which time reaction was checked *via* TLC analysis (see below). Once complete, the reaction was diluted with ether and stirred for ~5-10 min, followed by

direct transfer to an appropriately sized plug of silica gel / Celite / sand / Celite / sand, eluting with ether. After concentration under vacuum the resulting crude oil was then subjected to column chromatography on silica gel eluting with pentanes, then 3%, then 5% (ether : hexanes) to afford the title compound as a clear colorless oil, 36-44%.

***Note:** If, after initial filtration and concentration of the crude reaction mixture, deep coloration or significant salt presence is observed the crude material was passed through a second plug, as above.

***Note:** If silica gel purification is performed on 'activated' boronates, the material should pass through the column within 20 min at most. Otherwise, potential (most likely) protodeborylation will occur.

***Note:** It is common for sp- and sp^2-derived boronates to not produce (at least not significantly) a ^{13}C carbon response for the 'carbon' atom adjacent to the boronate; however, we have observed that sp^3 carbons attached to boron do give expected signals in their carbon NMR.

TLC: R_f = 0.21 (7% ether : hexanes), UV, I_2, $KMnO_4$ stain

^1H NMR: (500 MHz, $CDCl_3$) δ 6.68 – 6.23 (m, 1H), 4.19 – 4.14 (q, *J* = 7.2 Hz, 2H), 2.16 (s, 3H), 1.28 – 1.25 (m, 15H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 166.3, 130.7, 84.3, 59.9, 24.9, 16.4, 14.4

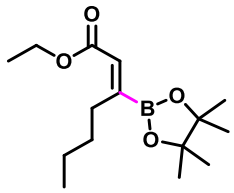
IR: 2990, 2930, 1719, 1361, 1322, 1256, 1189 cm^{-1}

HRMS: (EI) calculated for $[C_{12}H_{21}{}^{11}BO_4]$: 240.1533 $[M]^{+\bullet}$, found 240.1528

(E:Z): > 20:1 , see section with spectral data

Ethyl (*Z*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-2-enoate

Notebook: DJL-5-237



***Note:** Silica gel purification should be performed within 10-15 min at most. Otherwise, potential (highly likely) protodeborylation will occur.

Purification: column chromatography on silica gel eluting with hexanes, then 1% then 2% (ether : hexanes), clear colorless oil, 50%.

TLC: R_f = 0.40 (7% ether : hexanes), UV, I_2, $KMnO_4$ stain

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.39 (s, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 2.65 (t, *J* = 7.5 Hz, 2H), 1.42 – 1.30 (m, 4H), 1.29 – 1.24 (m, 15H), 0.89 (t, *J* = 7.3 Hz, 3H)

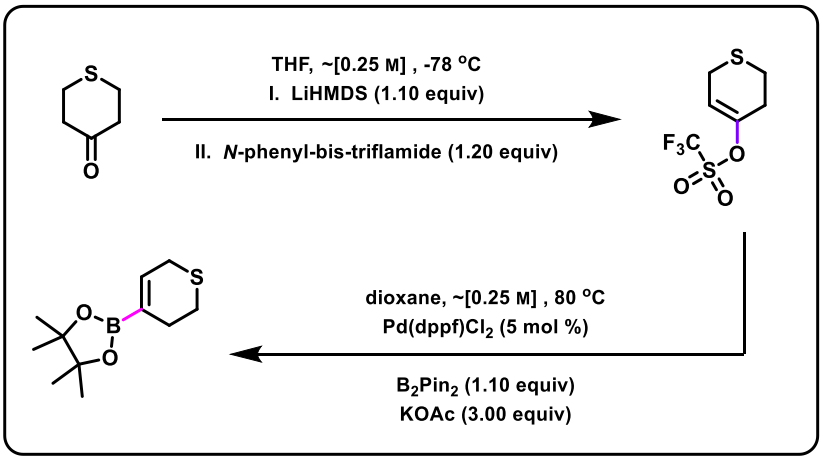
^{13}C NMR: (126 MHz, $CDCl_3$) δ 166.2, 129.9, 84.1, 59.9, 32.0, 29.9, 24.8, 23.0, 14.4, 14.2

IR: 2979, 2935, 2863, 1719, 1455, 1366, 1322 cm^{-1}

HRMS: (EI) calculated for $[C_{15}H_{27}{}^{10}BO_4]$: 281.2039 $[M]^{+\bullet}$, found 281.2030

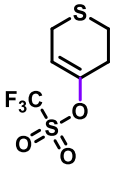
(E:Z): > 20:1 , see section with spectral data

1.3.2 Ketone derived boronates [8]



3,6-Dihydro-2*H*-thiopyran-4-yl trifluoromethanesulfonate

Notebook: DJL-6-171



To a clean and dry BRF charged with a stir bar and containing the corresponding ketone, in dry THF, ~[0.25 M], at -78 °C, was added LiHMDS (1.10 equiv.) in one portion as a solid. Stirring was continued at this temperature for 2 h at which point *N*-phenyl-bis-triflamide (1.20 equiv) was introduced in one portion as a solid. The reaction mixture was allowed to warm to rt over the course of ~12 h at which point TLC analysis indicated completion. The reaction was then quenched with saturated aqueous ammonium chloride and extracted with ether (x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was subsequently purified *via* column chromatography on silica gel, eluting with 10% (ether : hexanes), to afford the desired compound as a clear colorless oil, 85%.

TLC: R_f = 0.51 (20% ether : hexanes), UV, I_2

^{1}H NMR: (600 MHz, $CDCl_3$) δ 5.99 (t, *J* = 4.2 Hz, 1H), 3.32 – 3.27 (m, 2H), 2.85 (t, *J* = 5.7 Hz, 2H), 2.61 (m, 2H)

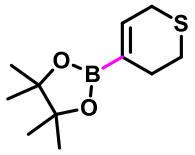
^{13}C NMR: (151 MHz, $CDCl_3$) δ 150.2, 119.7, 117.5, 117.1, 29.4, 25.3, 25.0

IR: 2913, 2830, 1691, 1410, 1196 cm^{-1}

HRMS: (EI) calculated for [$C_6H_7O_3S_2F_3$]: 247.9789 $[M]^{+\bullet}$, found 247.9787

2-(3,6-Dihydro-2*H*-thiopyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Notebook: DJL-6-173



A clean and dry RBF was taken into am argon filled glove box and charged with Pd(dppf)Cl_2 (5 mol %), B_2Pin_2 (1.10 equiv) and KOAc (3.00 equiv). Outside the glove box dry dioxane was added to the flask, ~[0.25 M], with stirring, followed by the corresponding alkenyl triflate. The flask was then fitted with an air condenser and stirred at 80 ^oC for 2 h, under argon. After cooling to rt, TLC analysis had indicated complete consumption of starting triflate, the reaction flask was transferred to a separatory funnel with ether and DI water, and the aqueous phase was extracted with ether (x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was subsequently purified *via* column chromatography on silica gel, eluting with 5% (ether : hexanes), to afford the desired compound as a viscous bronze oil which became a crystalline light orange/ yellow solid upon storage under high vac, 80%.

TLC: R_f = 0.46 (20% ether : hexanes), UV, I_2

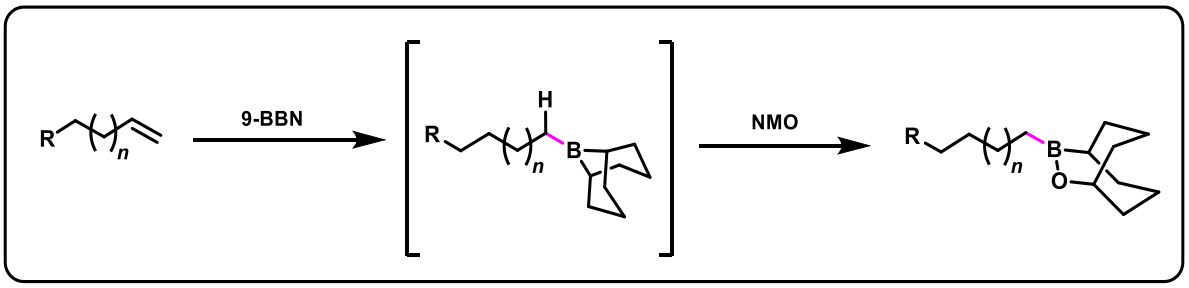
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.67 (dq, *J* = 6.0, 2.0 Hz, 1H), 3.20 (m, 2H), 2.68 (t, *J* = 5.8 Hz, 2H), 2.40 (m, 2H), 1.25 (s, 12H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 138.0, 83.5, 26.5, 26.4, 25.2, 24.9

IR: 2979, 2913, 1631, 1388, 1339 cm^{-1}

HRMS: (EI) calculated for $[C_{11}H_{19}{}^{10}BO_2S]$: 225.1235 $[M]^{+\bullet}$, found 225.1233

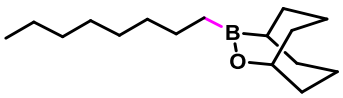
1.3.3 -OBBD boronic derivatives [9]



Prepared according to the method of Soderquist,[9] substituting trimethylamine-*N*-oxide with NMO (*N*-methylmorpholine oxide). Once reactions were complete the residue was concentrated under reduced pressure, re-suspended in ether and filtered through a short plug of silica gel to remove traces of *N*-methylmorpholine. The resulting –OBBD derivatives were used without further purification, and stored with, Teflon sealed, tightly capped vials, under argon, at 5 ^{o}C.

(1*s*,5*s*)-10-Octyl-9-oxa-10-borabicyclo[3.3.2]decane

Notebook: RTHL-6-289



TLC: R_f =0.32 (100% pentanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.73 – 4.15 (m, 1H), 1.92 – 1.19 (m, 25H), 0.91 – 0.85 (m, 3H), 0.85 – 0.71 (m, 2H)

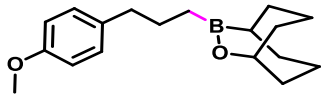
^{13}C NMR: (126 MHz, $CDCl_3$) δ 73.4, 33.0, 32.1, 32.0, 29.8, 29.5, 26.2, 24.2, 22.9, 22.5, 14.3

IR: 2924, 2858, 1702, 1455, 1416 cm^{-1}

HRMS: (EI) calculated for [$C_{16}H_{31}{}^{11}BO_2$] : 266.2417 [M+O]$^+$, found 266.2423

(1*s*,5*s*)-10-(3-(4-Methoxyphenyl)propyl)-9-oxa-10-borabicyclo[3.3.2]decane

Notebook: RTHL-7-012



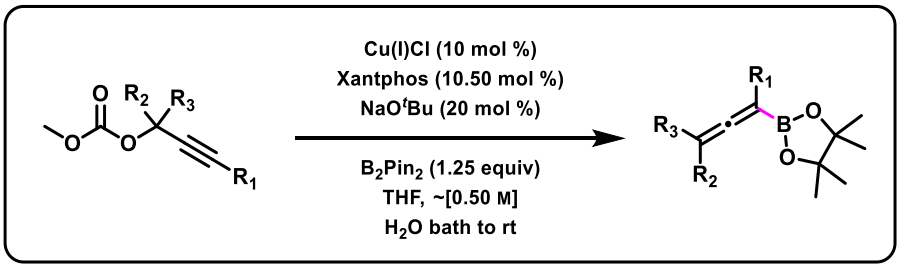
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.15 – 7.07 (d, *J* = 9.0 Hz, 2H), 6.87 – 6.80 (d, *J* = 8.5 Hz, 2H), 4.78 – 4.38 (m, 1H), 3.80 – 3.78 (bm, 3H), 2.60 – 2.48 (t, *J* = 7.8 Hz, 2H), 1.88 – 1.36 (m, 17H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.7, 135.5, 129.5, 113.7, 73.5, 55.4, 38.2, 32.0, 26.5, 26.1, 22.5

IR: 2924, 2858, 1614, 1510, 1300, 1240 cm^{-1}

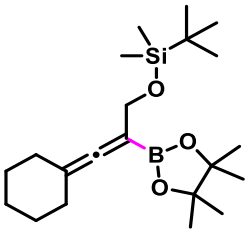
HRMS: (EI) calculated for [$C_{18}H_{27}{}^{10}BO_3$]: 301.2090 [M+O]$^+$, found 301.2097

1.3.4 Allenyl boronate synthesis *via* copper catalyzed S_N2[1] [10]



***tert*-Butyl((3-cyclohexylidene-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)ally-l)oxy)dimethylsilane**

Notebook: DJL-6-029



To a clean and dry BRF was added CuCl (10 mol %), Xantphos (10.50 mol %) and NaO-*t*-Bu (20 mol %) in a glove box. The sealed RBF was then removed from the glove box and dry THF, ~[0.50 M], was added slowly, washing the walls of the flask to bring all of the salts into solution; this solution was then stirred at rt for ~20 – 30 min. Then the flask was immersed in a rt water bath, followed by the addition of B_2Pin_2 (1.25 equiv) in one portion. The RBF's walls were washed with minimal THF with continued stirring for ~15 – 20 min. Then a solution of the methyl propargyl carbonate (1.00 equiv) in THF, ~[1.0 M], was added dropwise; the resulting reaction mixture was allowed to stir overnight, ~12-16 h (at rt) at which time the progress of the reaction was checked *via* TLC analysis (see below). Once complete, the reaction was diluted with ether and stirred for ~5-10 min, followed by direct transfer to an appropriately sized plug of silica gel / Celite / sand / Celite / sand, eluting with ether. After

concentration under vacuum the resulting crude oil was then subjected to column chromatography on silica gel eluting with 7% (ether : hexanes), followed by extended time at high vacuum (vial wrapped in aluminum foil). This afforded the title compound as a white crystalline solid, 55%.

***Note:** Silica gel purification should be performed within 10-15 min at most. Otherwise, potential (highly likely) protodeborylation will occur.

TLC: R_f = 0.56 (20% ether : hexanes), UV, I_2, vanillin stain (blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.19 (s, 2H), 2.14 (t, J = 6.0 Hz, 4H), 1.66 – 1.61 (m, 2H), 1.50 (m, 4H), 1.24 (s, 12H), 0.90 (s, 9H), 0.08 – 0.04 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 207.0, 100.0, 83.3, 63.2, 30.8, 27.5, 26.4, 26.2, 24.9, 18.5, -4.9

IR: 2979, 2930, 2856, 1951, 1757, 1427, 1350, 1256 cm^{-1}

HRMS: (EI) calculated for $[C_{17}H_{30}{}^{10}BO_3Si]$: 320.2094 $[M\text{-}C_4H_9]^+$, found 320.2093

1.4 Preparation of vinyl allenoates

1.4.1 Titration of commercial vinylmagnesium chloride.

Vinylmagnesium chloride was titrated by the following modification of Watson & Easthams procedure: 1,10-phenanthroline was dissolved in anhydrous xylenes to make a 1.5 mg/mL solution that served as indicator. The 1,10-phenanthroline solution (0.1 mL) and 0.9 mL of anhydrous xylenes were added to a dry 25 mL round bottom flask fitted with a septum, argon needle, and stir bar, and the flask was cooled to 0 °C in an ice bath. The Grignard reagent (1 mL) was drawn into a syringe and the first few drops of RMgX solution were added to the indicator resulting in a brightly colored solution which was stirred at 0 °C for 15 min. The absence of any loss in color indicated that the argon manifold was sufficiently anhydrous for subsequent work with organometallics. The remainder of the Grignard solution was added and let stir for a few minutes, then titrated dropwise at 0 °C with a [1.0 M] solution of 1-octanol in xylenes, whereupon the loss of color indicated the endpoint had been reached.

***Notes:**

1. Octanol was chosen as it is not very hygroscopic and led to minimal solubility problems associated with the resulting magnesium alkoxide. Additionally, the use of a primary alcohol over a secondary alcohol, while leading to a more exothermic reaction, conveniently gave a more rapid color change near the endpoint, with less stirring time needed between drops.
2. Switching the order of addition of RMgX/octanol did not give as satisfactory an endpoint; adding the octanol solution last is recommended.
3. Octanol and xylenes were dried over activated 3Å sieves overnight.

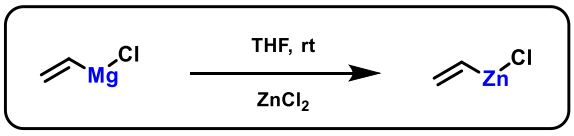
4. A [1 M] solution of octanol was prepared from 15 mL octanol and 80 mL xylenes.
5. Attempts to prepare vinylmagnesium chloride in diethyl ether by evaporating the THF at 0 °C under high vacuum, and exchanging the solvent, led to polymerization of the Grignard reagent. Additionally, attempts to prepare vinylmagnesium bromide in diethyl ether, as opposed to THF, were completely unsuccessful, regardless of quality or method of activation of the magnesium surface, and commercial vinylmagnesium chloride from Acros was used in this study. This surprising result has been noted previously. [11]
6. Grignard reagent was stored at ambient temperature under argon, and no substantial degradation in quality or titre was noticed over the course of this study.
7. No difference in titre was noticed performing the titration at ambient temperature using a water bath.

1.4.2 Preparation of [0.5 M] $ZnCl_2$ in THF

Zinc chloride was dried initially in an oven at 180 °C overnight, then transferred to a dry round bottom flask. The flask was placed under high vacuum with the aid of a dry ice/acetone trap and gently melted under low flame. The flask was let cool to allow solidification, and the process was repeated twice to give anhydrous $ZnCl_2$. Once cooled the flask was backfilled with argon and brought into to a glove box, along with a 100 mL volumetric flask, spatula, mortar and pestle, where the zinc chloride was ground to a fine powder and 6.816 g (50 mmol) were weighed out into the 100 mL volumetric flask. The volumetric flask containing the $ZnCl_2$ was fitted with a septum and brought out of the glove box, and anhydrous THF was added *via* cannula to make the final volume 100 mL, the septum was briefly removed under argon to add a clean, dry, stir bar and the flask was stirred vigorously to give a [0.5 M] solution of $ZnCl_2$ in THF.

1.4.3 Vinyl zinc chloride

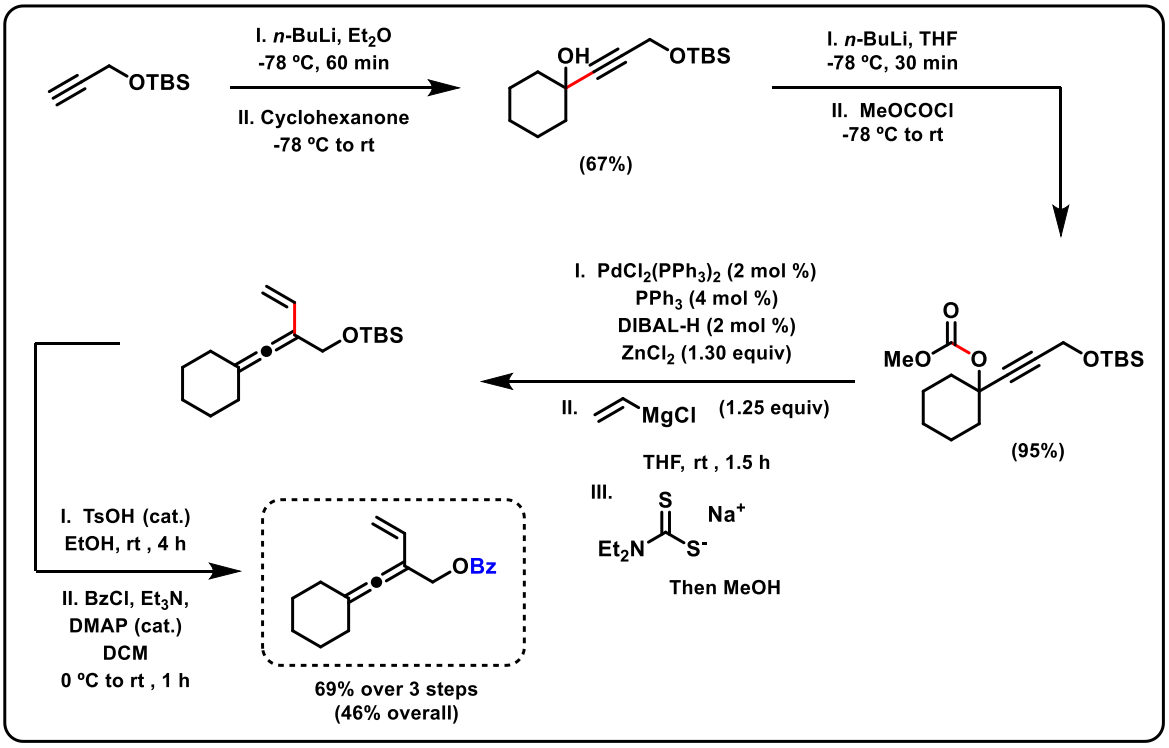
Notebook: RTHL-7-139



Vinylmagnesium chloride (24 mmol) in THF (15 mL, titrated to [1.6 M] by the aforementioned method) was added *via* syringe to a dry 100 mL round bottom flask fitted with a stir bar, septum, and argon needle, and placed in a water bath. $ZnCl_2$ (24 mmol, 48 mL, [0.5 M]) in THF was introduced slowly *via* syringe and the solution was stirred for 3 h at rt to give a tan solution of vinylzinc chloride (assumed to be [0.38 M]) with some precipitate. Stirring

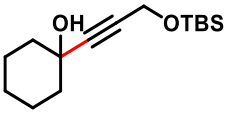
was stopped to let the precipitate settle, and the supernatant could be then used directly in subsequent Negishi couplings. Alternatively, the majority of the precipitated salts could be filtered off by means of a double ended frit into a fresh 100 mL flask under argon.

1.4.4 Synthesis of vinyl allenoate and intermediates



1-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-yn-1-yl)cyclohexan-1-ol

Notebook: RTHL-7-162-(top)



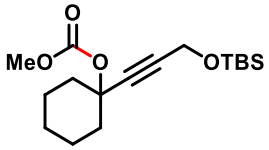
To a dry 1 L round bottom flask fitted with a septum, stir bar, and argon needle was added 17.714 g (104 mmol, 1.04 equiv) of TBS-protected propargyl alcohol, and 500 mL anhydrous Et_2O. The solution was cooled with stirring to -78 ˚C in a dry ice/acetone bath

whereupon 44 mL of *n*-BuLi [2.35 M] in hexanes (103.4 mmol, 1.034 equiv) was added dropwise over *ca*. 15 min, and the solution was stirred for 1 h at this temperature. Freshly distilled cyclohexanone (10.35 mL, 100 mmol, 1 equiv) was added slowly dropwise, and once the addition was complete the solution was stirred at -78 ˚C for an additional 1-2 h whereupon the cooling bath was removed, and the flask was stirred while gradually warming to rt with slight yellowing of the solution. Once the solution reached ambient temperature, the septum was removed, and the reaction was quenched by the ***cautious*** addition of 100 mL of a dilute pH 7 buffer solution. The mixture was stirred vigorously for a few min, then let settle before decanting the ether layer into a separatory funnel, with an additional 200 mL of ether used to rinse the reaction flask. The organic layer was extracted with DI water (50 mL x 2), brine (x 1), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to afford a crude oil. The crude compound was then placed under high vacuum and let sit for 3 d in this manner with periodic rotation of the flask to remove traces of cyclohexanone. Unreacted cyclohexanone could not be satisfactorily removed by chromatography owing to the small differences in polarity, and if present, the use of a high vacuum manifold is recommended. Once traces of cyclohexanone were fully removed, as indicated by TLC (R_f = 0.16, 10% (Et_2O : hexanes), yellow-green spots with vanillin), the crude material was loaded with hexanes onto a flash column and purified by gradient elution (0-2-5-25%, Et_2O : hexanes). Fractions containing the desired material were pooled, evaporated with pentanes under reduced pressure, affording a clear viscous oil which gradually solidified into an amorphous white solid upon standing under high vacuum. Yield was 18 g (67%).

***Although prepared in a slightly different manner, analytical data is identical with the same molecule prepared above.

1-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-yn-1-yl)cyclohexyl methyl carbonate

Notebook: RTHL-7-162-(bottom)



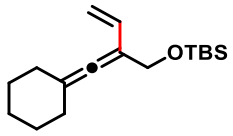
A dry 250 mL round bottom flask fitted with a septum, stir bar, and argon needle, was charged with 8.215 g of tertiary alcohol (30.6 mmol, 1.02 equiv) and 130 mL of anhydrous THF and stirred at rt until complete dissolution. The flask was cooled with stirring to -78 ˚C, in a dry ice/acetone bath and let stir for 10-15 min. *n*-BuLi (2.35 M in hexanes; 12.9 mL, 30.3 mmol, 1.01 equiv) was then added slowly dropwise via syringe, and the solution was stirred for an additional 30 min while maintaining a -78 °C temperature. Methyl chloroformate (2.318 mL, 30 mmol, 1.00 equiv) was added slowly dropwise *via* syringe, and the solution was stirred for an additional 1 h at -78 ˚C. The cooling bath was then removed and let stir while warming to rt over the course of 2 h. The septum was then removed, and the reaction was quenched with 25 mL of sat. aqueous $NaHCO_3$ and 25 mL of DI water and stirred vigorously for 30 min to remove any traces of unreacted chloroformate. The stir bar was then removed, and the majority of the volatiles were evaporated under reduced pressure. The contents of the flask were then poured into a separatory funnel, and the flask was rinsed with two 100 mL portions of ether into the separatory funnel and shaken. The layers were separated, and the ether layer was washed with a small quantity of DI water, saturated aqueous$NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and evaporated to obtain a crude oil. The crude material was loaded on a silica column with hexanes, and purified by gradient elution, 0-5-10-100% (Et_2O : hexanes). Fractions were pooled and evaporated with pentanes under reduced pressure, then let stand

under high vacuum to afford the title compound as a clear viscous oil. Yield was 9.365 g (95.6%).

***The title compound was prepared by an adaptation of a published procedure. [12]

***tert*-Butyl((2-(cyclohexylidenemethylene)but-3-en-1-yl)oxy)dimethylsilane**

Notebook: RTHL-7-169-A



Reaction Set-Up:

A dry 500 mL round bottom flask was fitted with a stir bar, septum, taken into a glove box where 7.083 g $ZnCl_2$ (52 mmol, 1.3 equiv, **Note 1**), 561 mg $PdCl_2(PPh_3)_2$ (0.8 mmol, 0.02 equiv), and 419 mg PPh_3 (1.6 mmol, 0.04 equiv, **Note 2**), were added. The flask was sealed and removed from the glove box, placed under a positive pressure of argon, 400 mL anhydrous THF were added and the solution was stirred at rt until complete dissolution of all solids. DIBAL-H in hexanes ([1.0 M] solution, 0.8 mL, 0.8 mmol, 0.02 equiv) was added slowly *via* syringe with stirring whereupon the solution turned from yellow to a dark brown (**Note 3**). The flask was then placed in a water bath to maintain ambient temperature, and 31.25 mL of a [1.6 M] solution of vinylmagnesium chloride in THF (50 mmol, 1.25 equiv) was added slowly *via* syringe where there was a slight exotherm and formation of some precipitate (**Note 4**). After the addition was complete, the solution was stirred at rt for an additional 15 min to ensure complete formation of the zinc reagent. The propargyl carbonate (13.06 g, 40 mmol, 1.0 equiv) was then added rapidly *via* syringe whereupon there was a slight exotherm accompanied with

some effervescence (argon needle is still present to accommodate any pressure buildup of CO_2). The solution was let stir at rt for 1-1.5 h or until TLC indicated complete conversion.

***Proper quenching of the reaction mixture, precipitation of Mg/Zn salts, *and most importantly rapid removal of palladium residues*, are essential to obtain the desired vinylallene in high yield/purity. Incomplete removal of Pd residues before chromatography were found to substantially degrade the desired product and make separation tedious (**Note 5**).

Reaction Work-Up:

Methanol (3 mL) was then added *via* syringe to quench excess organometallics, and the solution was stirred for a few minutes, the septum was briefly removed and 4 g of sodium diethydithiocarbamate trihydrate (NaDEDTC) was added in one portion, and the vessel resealed and stirred for an additional 10 min. Then, 100 mL of hexanes was added with stirring resulting in the precipitation of a large amount of salts, and the solution was quickly filtered over a short pad of silica gel into a 1 L round bottom flask, and the residue in the reaction flask was rinsed through the pad with additional ether. An additional 4 g of NaDEDTC, was added to the 1 L flask and the volatiles were removed under reduced pressure. The crude residue was re-suspended with ether being added to the flask, and the contents were filtered over a second pad of silica gel. NaDEDTC (4 g) and 100 mL of DI water were added to the solution, and the solution was transferred to a separatory funnel, where it was shaken, and the layers separated. The ether layer was washed with an additional portion of DI water, then brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give a crude yellow oil with some yellow precipitate. The crude material was *immediately* taken up in hexanes and loaded onto a silica column and purified by gradient elution (0-1-2-5%, Et_2O : hexanes). Under

these conditions the desired product was incompletely separated from traces of PPh_3 but could be used without disadvantage in the subsequent reaction. Pure fractions were combined and evaporated and weighed 6.8 g (59.6%). The mixed fractions containing product and traces of PPh_3 were evaporated to yield an additional 3.6 g of material (31.6%). Both samples were combined for the following reaction.

TLC: R_f = 0.79 (2.5% ether : hexanes), UV, I_2, vanillin stain

^{1}H NMR: (500MHz, $CDCl_3$) δ (ppm): 6.22 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.21 (d, *J* = 17.5 Hz, 1H), 4.99 (d, *J* = 11.0 Hz, 1H), 4.31 (s, 2H), 2.20-2.10 (m, 4H), 1.65-1.50 (m, 6H), 0.90 (s, 9H), 0.07 (s, 6H)

^{13}C NMR: (125MHz, $CDCl_3$) δ (ppm): 200.28, 134.52, 112.27, 104.37, 103.46, 62.52, 31.38, 27.64, 26.26, 26.06, 18.49, -5.05

IR: 3089, 2924, 2847, 1944, 1609, 1251, 1069 cm^{-1}

HRMS: (CI) calculated for [$C_{17}H_{31}OSi$]: 279.2139 $[M]^{+\bullet}$, found 279.2133

*** Vinyl allene was prepared from the preceding carbonate by substantial modifications of Vermeer's procedure.[13]

Note 1: Although Vermeer's protocol uses, and our initial experiments were performed with, the preformed zinc reagent, it was found to be much more convenient to form the reagent *in situ*, with a slight excess of $ZnCl_2$ relative to RMgX, with 10-15 min of stirring sufficient to ensure complete formation of the organozinc.

Note 2: Vermeer's protocol recommends the use of $Pd(Ph_3P)_4$, however, owing to the oxygen sensitivity/batch variability of this reagent, more reliable results and cleaner reactions were obtained making it *in situ* from $Pd(PPh_3)_2Cl_2$ and PPh_3. Additionally, several other catalyst systems were examined, including Pd(0)/$(P(o\text{-tol})_3)_2$, Pd(0)/$(PCy_3)_2$, Neolyst CX-31, 1000 ppm HandaPhos/$PdCl_2$, IPrCuCl, and Pd(DPEPhos)Cl_2. Surprisingly PPh_3 is the preferred ligand for this transformation, with DPEPhos being the other ligand that gave any appreciable amount of product (*vide infra*). These results are in agreement with those of Molander who investigated the preparation of vinylallenes from vinyl-BF_3K salts and also found PPh_3 as the preferred ligand.[14]

Note 3: DIBAL-H was used to reduce Pd(II) to active Pd(0). While the vinyl organometallic could be used as well to reduce palladium, reductive elimination from this complex furnishes a small amount of 1,3-butadiene which could potentially react with desired product and/or lead to side reactions; hence, the use of DIBAL-H is recommended. Additionally, the use of DIBAL-H is required when using different Grignard reagents such as MeMgCl, which did not reduce Pd(II) in the presence of $ZnCl_2$, for *in situ* RZnX formation.

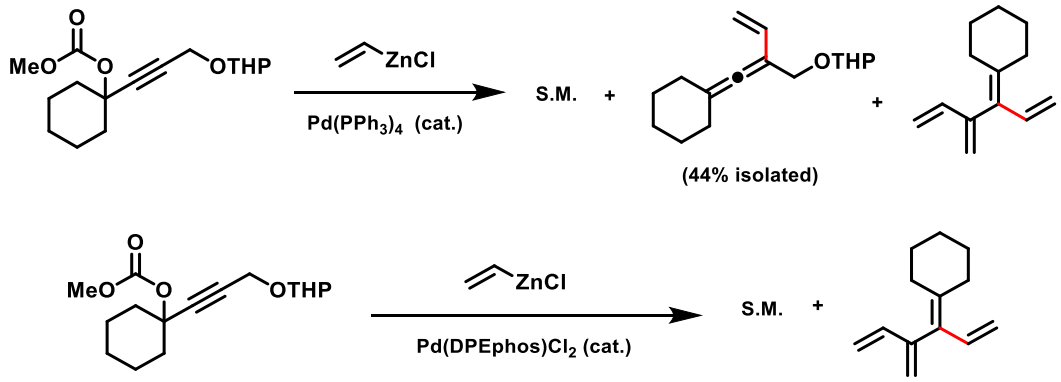
Note 4: An exotherm was observed but is not vigorous even if the addition rate is rapid and a water bath was employed.

Note 5: As noted by Molander,[14] if palladium residues are not rapidly removed at the end of the reaction, the yield suffers substantially with the formation of several byproducts similar in R_f to product, as well as some additional baseline impurities. Even several successive filtrations though silica gel at the end of the reaction are insufficient to remove soluble palladium species. Molander recommends the addition of activated charcoal (DARCO®) and stirring under air for

30 min followed by filtration over Celite, and while in their case this procedure was successful at preventing the majority of sample degradation, for us separation was still tedious to remove trace impurities, which unfortunately could not be separated at a later stage in the synthesis. Therefore, alternative methods were examined to remove the palladium residues presumably responsible for sample degradation.

Note 6: We were encouraged by a report detailing the use of sodium dithiocarbamate salts to remove metal residues, regardless of oxidation state, from organic mixtures to uniformly achieve <10 ppm levels of Pd, Cu, and Fe in API's.[15] Gratifyingly, the use of three successive treatments with NaDEDTC combined with two silica gel filtrations, and an aqueous workup, provided a crude material with substantially improved yield and impurity profile. While likely excessive, the procedure was not optimized to reduce the number of filtrations or determine the minimum amount of NaDEDTC required for full Pd removal.

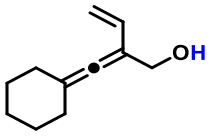
Note 7: Reaction of the analogous OTHP ether in place of the OTBS derivative gave in addition to anticipated product, unreacted starting material and a [4]dendralene as the major side product as identified by ^{1}H NMR. Switching the catalyst to Pd(DPEPhos)Cl_2 led to the formation of the [4]dendralene to the exclusion of the vinylallene. The catalyst Pd(DPEPhos)Cl_2, therefore, kinetically favors reaction with the OTHP-vinylallene intermediate over the starting propargyl carbonate.



Note 8: Attempts to install the vinyl unit on allenes *via* cuprates were low yielding. See sub-section 2.4.5, below, for additional details.

2-(Cyclohexylidenemethylene)but-3-en-1-ol

Notebook: RTHL-7-169-B



The aforementioned vinylallene (10.4 g) was dissolved in 200 mL of absolute EtOH in a 500 mL round bottom flask with a stir bar, followed by 1.384 g of *p*-toluenesulfonic acid monohydrate (7.28 mmol, 0.2 equiv; **Note 1**) and the solution was sealed with a septum and stirred for *ca*. 4 h at rt until there was no further change as evidenced by TLC (**Note 2**). Solid $NaHCO_3$ (10 mmol) was added along with 50 mL of DI water to quench the reaction, and the EtOH was removed under reduced pressure. The contents of the flask were poured into 200 mL of ether in a separatory funnel, the reaction flask was rinsed with additional ether, and the layers were separated. The ether layer was washed sequentially with additional DI water, saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and evaporated under

reduced pressure to afford crude allenyl alcohol which was purified further by flash chromatography gradient elution 0-5-10-20% (Et_2O : hexanes) (**Note 3**). Evaporation of factions afforded vinylallenol as a clear to slightly yellow oil with a pungent sweet odor. Yield was 5.86 g (93%) and was observed by NMR to contain *ca*. 5% of TBS-OH that co-eluted with product. The product was stored under high vacuum in a dry round bottom flask overnight before being carried into the next step.

TLC: R_f = 0.25 (20% ether : hexanes), UV, I_2, vanillin stain

^{1}H NMR: (500 MHz, $CDCl_3$) δ: 6.26 (dd, *J* = 18.5, 11.0 Hz, 1H), 5.14 (d, *J* = 18.5 Hz, 1H), 5.01 (d, *J* = 11 Hz, 1H), 4.23 (s, 2H), 2.18-2.14 (m, 4H), 1.65-1.50 (m, 7H)

^{13}C NMR: (125MHz, $CDCl_3$) δ: 198.15, 133.83, 112.21, 107.89, 104.16, 60.50, 31.59, 27.83, 26.12, 25.77

IR: 3410, 2923, 2856, 1937, 1699, 1444 cm^{-1}

HRMS: (CI) calculated for [$C_{11}H_{16}O$] : 164.1201 $[M]^{+\bullet}$, found 164.1195

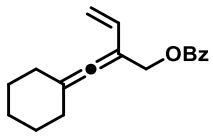
Note 1: PTSA was found to be a convenient and efficient acid catalyst for this desilylation. The use of pyridinium *p*-toluenesulfonate (PPTS) as a milder acid catalyst had no benefit in terms of reaction cleanliness, and longer reaction times and/or heating was required. The use of Dowex 50-W as a heterogeneous acid catalyst, even at high loadings, gave a much slower reaction than PTSA.

Note 2: Residual starting material stains very intensely under UV/I_2 and trace amounts of starting material can appear as significant quantities. A reaction time of *ca*. 4 h is usually sufficient to desilylate the majority of substrate.

Note 3: A 0-5% portion of the gradient elution is necessary to remove traces of starting material, and the residual PPh_3 present in the starting material.

2-(Cyclohexylidenemethylene)but-3-en-1-yl benzoate (19)

Notebook: RTHL-7-167



The flask containing *ca*. 33.8 mmol vinylallenol from the preceding step was back-filled with argon, removed from the manifold and quickly fitted with a dry stir bar, septum, and argon needle. Anhydrous DCM (25.5 mL) was added *via* syringe, followed by anhydrous Et_3N (14.22 mL, 101.5 mmol, 3 equiv) and DMAP (68 mg). The flask was cooled to 0 ˚C in an ice bath and stirred gently for 10 min. Benzoyl chloride (5.9 mL, 50.8 mmol, 1.5 equiv) was then added slowly dropwise *via* syringe over 10 min, during which time some white precipitate was observed along with a yellowing of the solution. The solution was stirred at 0 ˚C for an additional 15 min, and the cooling bath was then removed and let stir while warming to rt for an additional 45 min. Once TLC indicated that the reaction was complete, the reaction was diluted with 200 mL ether, and <u>*cautiously*</u> poured into 100 mL saturated aqueous $NaHCO_3$ in a 500 mL round bottom flask, rinsing the reaction flask with additional ether. The biphasic solution was stirred vigorously at rt until TLC indicated that the excess benzoyl chloride had been completely quenched. The contents were then transferred to a separatory funnel, rinsing the flask with additional ether and the layers were separated. The organic layer was then washed sequentially with 70 mL DI water (*ca*. 2 mL/mmol), twice with 100 mL (10% w/w) aqueous $NaHSO_4$ (*ca*. 3 mL/mmol), 70 mL DI water, and finally 70 mL (2 mL/mmol) of sat.

aqueous $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to afford crude compound as a viscous yellow oil. The crude material was then azeotroped twice with pentanes to remove traces of Et_3N and Et_2O that interfered with subsequent chromatography, causing product to elute too rapidly. The crude material was loaded onto a flash column with hexanes, and purified by gradient elution 0-2% (Et_2O : hexanes). The fractions containing desired material were pooled, concentrated under reduced pressure, and trace volatiles were removed under high vacuum for several hours giving the pure vinylallenyl benzoate as a viscous, clear to faintly yellow oil. Yield was 7.4 g (81%). This compound was stored under argon, protected from light, in vials tightly wrapped with parafilm.

TLC: R_f = 0.61 (5% ether : hexanes), UV, I_2, vanillin stain

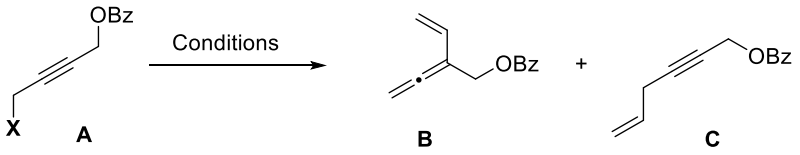
^{1}H NMR: (500MHz, $CDCl_3$) δ: 8.07-8.05 (m, 2H), 7.57-7.53 (m, 1H), 7.45-7.43 (m, 2H), 6.30 (dd, *J* = 18.0, 11.0 Hz, 1H), 5.21 (d, *J* = 17.5 Hz, 1H), 5.05 (d, *J* = 11.0 Hz, 1H), 4.98 (s, 2H), 2.17-2.08 (m, 4H), 1.62-1.42 (m, 6H)

^{13}C NMR: (125MHz, $CDCl_3$) δ: 201.24, 166.39, 134.02, 132.98, 130.56, 129.80, 128.41, 112.33 105.49, 99.06, 63.16, 31.15, 27.35, 26.05

IR: 2919, 2852, 1955, 1713, 1449, 1267, 1102 cm^{-1}

HRMS: (CI) calculated for [$C_{18}H_{19}O_2$]: 267.1380 $[M-H]^+$, found 267.1405

1.4.5 Selected optimization conditions for vinylallenyl-benzoate formation *via* cuprates



Entry	M (equiv.)	X	Cu (equiv.)[a]	Solvent	Temp.	A	B	C	Method[b]
1	MgCl (1.00)[c]	OBz	CuI (1.00)	THF [0.2M]	-30ºC	100	0	0	(TLC)
2	--	--	CuI•PPh_3 (1.00)	--	--	100	0	0	(TLC)
3	--	--	CuBr•LiI (1.00)[d]	--	-30ºC to rt.	100	0	0	(TLC)
4	--	OMs	CuCN•2LiCl (1.00)	--	-78ºC	80	5	15	(GCMS)
5	--	--	--	Et_2O [0.2M]	--	0	25	25	(TLC)
6	**--**	**Cl**	**--**	**--**	**--**	**(45% iso. as 4:1 mixture of B:C)**			**(^{1}H-NMR)**
7	Li **(1.00)**	**--**	**[(2-Thienyl)CuCN]$^-$ Li$^+$ (1.00)**	**THF [0.2M]**	**--**	**(32% pure B isolated)[e]**			**(^{1}H-NMR)**
8	--	--	CuCN (1.00)	--	--	100	0	0	(TLC)
9	Li (2.00)	--	--	--	--	0	0	42	(^{1}H-NMR)
10	**MgCl (1.10)[c]**	**--**	**CuCN•2LiCl (0.10)[f]**	**Et_2O [0.2M]**	**-78ºC to rt.**	**(23% pure B isolated)[e]**			**(^{1}H-NMR)**

-- denotes no change from the variable given above.
Reactions were stirred until TLC indicated no further change in conversion (typically 2-18 hours).

[a] Reactions with stochiometric Cu were performed by first adding the indicated organometallic to the copper source, to form either "RCu" or the cuprate. Once reagent was fully formed the substrate was introduced last.

[b] Conversion as determined by TLC, GCMS, or ^{1}H-NMR. TLC values are approximate.

[c] Vinylmagnesium chloride was added as a [1.6M] solution in THF.

[d] With 1 equiv. BF_3•Et_2O to give formally RCu•BF_3 (Yammamoto's Reagent)

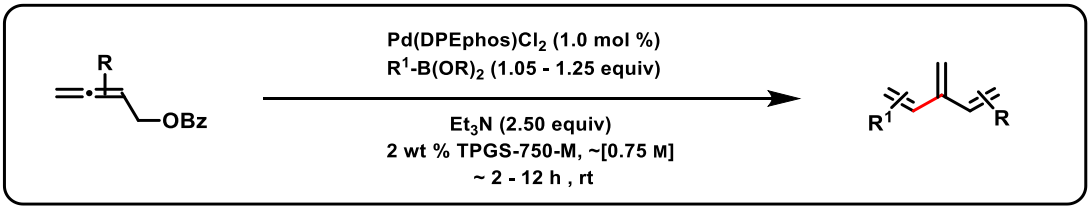
[e] Regioisomer **C** was present in small amounts as indicated by TLC and content was not determined. Yield refers to isolated amount of pure **B** after chromatography, mixed fractions containing **B**+**C** were discarded and not factored into the reported yield.

[f] RMgX was introduced last down the sides of the reaction vessel (1 drop/5 seconds) to a solution of copper catalyst and substrate at -78ºC.

Initially it was anticipated that desired vinylallenyl-benzoates could be formed *via* an S_N2' reaction of vinylcuprates with propargylic electrophiles. Extensive attempts to optimize the reaction were for the most part unsuccessful, and a sample of the many conditions tested are reported above. Vinylallenyl-benzoates could only be formed from the corresponding chloride in low yield by either: the stochiometric mixed magnesio-cynaocuprate in ether (entry **6**), *via* the stoichiometric mixed higher order cyanocuprate in THF (entry **7**), or using the Grignard reagent with a catalytic amount of the soluble CuCN•2LiCl in ether (entry **10**). In general, higher S_N2' selectivity was observed in Et_2O as opposed to THF, yet vinylmagnesium reagents cannot be prepared in Et_2O (*vide supra*), and as a result, regioselectivity suffers. These approaches were on the whole unsatisfactory as they generated a large amount of copper and cyanide waste, required cryogenic temperatures, overall yields were low, and chromatographic separation of regio-isomeric product **C** was tedious. Therefore, this route was abandoned in favor of the aforementioned Negishi coupling route that proved superior in all respects.

2. General Methods for Dendralene Synthesis

2.1.1 Suzuki-Miyaura-mediated synthesis: General procedure 'A'

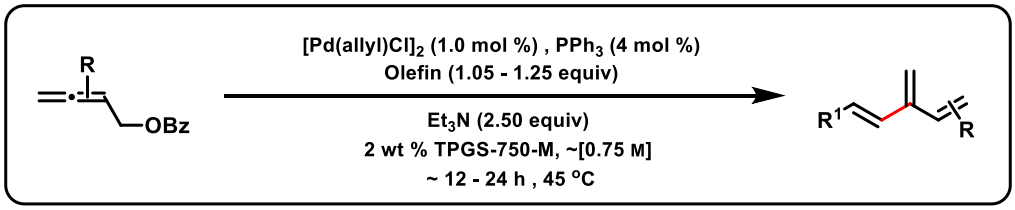


Into a screw cap vial was measured the desired allenoate (1.00 equiv) followed by Pd(DPEphos)Cl_2 (≤1 mol %). To this vial was then added a 2 wt % solution of TPGS-750-M in DI water to arrive at a ~ [0.75 M] solution and the reaction mixture was stirred with a strong vortex at rt. Then 'a few drops' of Et_3N were added (to aid in reaction homogeneity, and possibly facilitating initial reduction of the Pd(II) catalyst to the active Pd(0) species) followed by addition of the boron coupling partner (1.05 – 1.25 equiv) either dropwise for oils or in one portion for solids, followed by the remainder of Et_3N (2.50 equiv total), rinsing any residue from the wall of the vial into solution. The reaction was capped and allowed to stir at rt for ~ 2–12 h. Upon complete consumption of allenoate *via* TLC analysis (see below) a small amount of EtOAc was added to the reaction and gently stirred for ~ 5–10 min (milky pale yellow/orange solution will eventually become clear yellow/orange). This mixture was directly passed through a short plug of Celite on top of silica gel with ether and concentrated *via* rotary evaporation. Purification by column chromatography on silica gel afforded the desired compound.

***Note:** The allenoate is usually added first *via* glass pipette capillary action. This is due to the highly viscous nature of most of the allenoates utilized in this research, making use of a

microliter syringe cumbersome and the use of a disposable syringe/needle impractical due to substantial, yet unavoidable, transfer losses of valuable material. However, reactions are typically unaffected by the order of addition as long as the boron coupling partner is added last because of eventual protodeborylation in an aqueous environment.

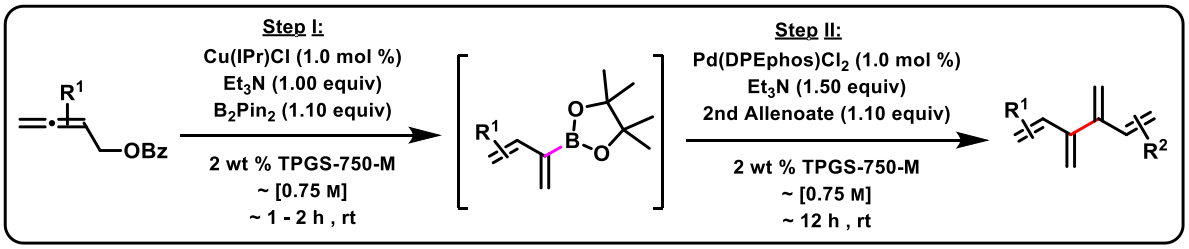
2.1.2 Heck-mediated synthesis: General procedure 'B'



To a screw cap vial was measured the desired allenoate (1.00 equiv), followed by $[Pd(allyl)Cl]_2$ (1 mol %) and PPh_3 (4 mol %). To this vial was then added a 2 wt % solution of TPGS-750-M in DI water to arrive at a ~ [0.75 M] solution and the reaction mixture was stirred with a strong vortex at rt. Then 'a few drops' of Et_3N were added followed by addition of the olefin (1.05 – 1.25 equiv), followed by the remainder of Et_3N (2.50 equiv total), rinsing any residue from the wall of the vial into solution. The reaction was capped and heated to 45 ^oC for ~12–24 h. Upon complete consumption of allenoate *via* TLC analysis (see below), a small amount of EtOAc was added to the reaction and stirred for ~5 – 10 min (milky pale white to grey solution will eventually become clear to light yellow tinted). This mixture was directly passed through a short plug of Celite on top of silica gel with ether and concentrated *via* rotary evaporation. Purification by column chromatography on silica gel afforded the desired compound.

***Note:** Once all reagents have been added, the reaction may also be performed at rt if the sealed, full, reaction mixture is slowly heated *via* heat-gun until the milky solution becomes transparently clear yellow/light orange. After stirring for ~ 12 h this process is again performed, and on the following day the reaction should be complete. However, it is advised, if possible, to maintain 45 ^{o}C throughout for a more robust reaction.

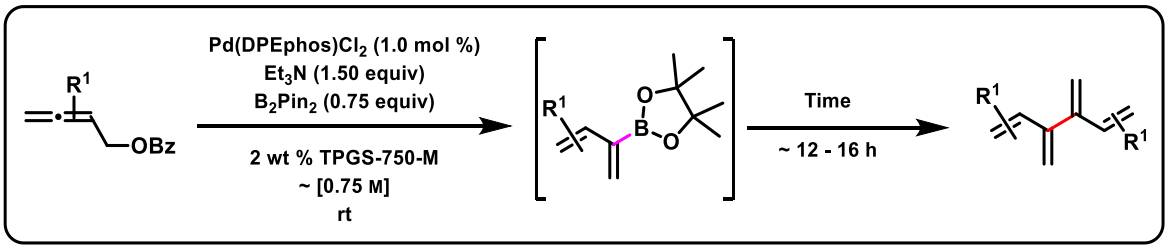
2.1.3 Tandem borylation-Suzuki approach [16] : General procedure 'C'



To a screw cap vial was measured the desired allenoate (1.00 equiv) followed by Cu(IPr)Cl (1 mol %). To this vial was then added a 2 wt % solution of TPGS-750-M in DI water to arrive at a ~[0.75 M] solution and the reaction mixture was stirred with a strong vortex at rt, Then a few drops of Et_3N were added followed by addition of B_2Pin_2 (1.10 equiv), in one portion, followed by the remainder of Et_3N (1.00 equiv total), rinsing any residue from the wall of the vial into solution. The reaction was capped and allowed to stir at rt for *ca*. 1-2 h. Upon complete consumption of allenoate *via* TLC analysis (see below) the reaction cap was removed, followed by sequential introduction of Pd(DPEphos)Cl_2 (≤1 mol %), the second allenoate (1.10 equiv) and more Et_3N (1.50 equiv total for this next step). The screw-cap was replaced and vigorous stirring was continued at rt for another 12 h. Once complete consumption of the allenic intermediate from the initial step (*i.e.*, the borylated 1,3-butadiene)

was observed *via* TLC analysis (see below) a small amount of EtOAc was added to the reaction after which it was stirred for *ca*. 5–10 min (milky pale yellow/orange solution will eventually become clear yellow/orange). This mixture was directly passed through a short plug of Celite on top of silica gel with ether and concentrated *via* rotary evaporation. Purification by column chromatography on silica gel afforded the desired compound.

2.1.4 Palladium / B_2Pin_2 mediated homocoupling: General procedure 'D'



To a screw cap vial was measured the allenoate (1.00 equiv, 0.50 equiv relative to mmol product) followed by Pd(DPEphos)Cl_2 (≤1 mol %, relative to mmol allenoate). To this vial was then added a 2 wt % solution of TPGS-750-M in DI water to arrive at a ~[0.75 M] solution and the reaction mixture was stirred with a strong vortex at rt. Then, half of the Et_3N (0.75 equiv, relative to mmol allenoate) was added followed by addition of B_2Pin_2 (0.75 equiv relative to mmol allenoate, 1.50 equiv relative to mmol product) in one portion, followed by the remainder of Et_3N (1.50 equiv total, relative to mmol allenoate), rinsing any residue from the wall of the vial into solution. The reaction was capped and allowed to stir at rt for *ca*. 12–16 h. Upon complete consumption of allenoate *via* TLC analysis (see below) a small amount of EtOAc was added to the reaction which was then stirred for *ca*. 5–10 min (milky pale yellow/orange solution will eventually become clear yellow/orange). This mixture was directly passed through a short plug of Celite on top of silica gel with ether and concentrated *via* rotary

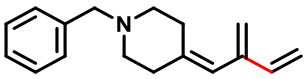
evaporation. Purification by column chromatography on silica gel afforded the desired compound.

***Note:** Half of the triethylamine was added up front to assure that B_2Pin_2 immediately goes into solution upon addition. Otherwise, 'clumping' of B_2Pin_2 was observed, along with poor stirring and yields were diminished as a result.

2.2 Product characterization

1-Benzyl-4-(2-methylenebut-3-en-1-ylidene)piperidine (1)

Notebook: DJL-6-094



Prepared according to general procedure **A**, 0.40 mmol scale.

Purification : column chromatography on silica gel, eluting with 10% (ether : DCM), light yellow viscous oil, 67 mg, 70%.

TLC: R_f = 0.39 (10% ether : DCM), UV, I_2, vanillin stain (purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 4H), 7.27 – 7.24 (m, 1H), 6.42 (dd, *J* = 17.0, 10.5 Hz, 1H), 5.77 (s, 1H), 5.25 – 5.21 (m, 1H), 5.18 (d, *J* = 2.0 Hz, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 4.96 (s, 1H), 3.52 (s, 2H), 2.52 – 2.49 (t, *J* = 5.5 Hz, 2H), 2.43 – 2.40 (m, 2H), 2.38 – 2.32 (m, 4H)

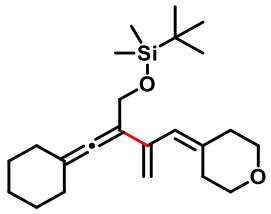
^{13}C NMR: (126 MHz, $CDCl_3$) δ 143.2, 141.1, 139.2, 138.7, 129.2, 128.3, 127.1, 119.9, 117.8, 115.3, 63.1, 55.4, 54.9, 36.3, 29.7

IR: 3084, 3034, 2935, 2897, 2797, 2759, 1730, 1587, 1449, 1278 cm^{-1}

HRMS: (EI) calculated for [$C_{17}H_{22}N$]: 240.1752 $[M+H]^+$, found 240.1758

***tert*-Butyl((2-(cyclohexylidenemethylene)-3-((tetrahydro-4*H*-pyran-4-ylidene)methyl)but-3-en-1-yl)oxy)dimethylsilane (2)**

Notebook: DJL-6-035-A



Prepared according to general procedure **A**, 0.30 mmol scale.

Purification: column chromatography on silica gel eluting with 5% then 10% (ether : hexanes), viscous colorless oil, 73 mg, 65%.

TLC: R_f = 0.50 (20% ether : hexanes), UV, I_2, vanillin stain (Pacific blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.20 (d, *J* = 1.5 Hz, 1H), 4.82 (s, 1H), 4.34 (s, 2H), 3.70 (t, *J* = 5.5 Hz, 2H), 3.61 (t, *J* = 5.5 Hz, 2H), 2.42 (t, *J* = 5.3 Hz, 2H), 2.26 (t, *J* = 5.0 Hz, 2H), 2.20 – 2.14 (m, 2H), 2.07 (m, 2H), 1.68 (m, 2H), 1.63 – 1.58 (m, 1H), 1.55 – 1.45 (m, 3H), 0.88 (s, 9H), 0.05 (s, 6H)

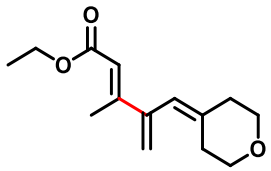
^{13}C NMR: (126 MHz, $CDCl_3$) δ 200.0, 140.1, 136.4, 124.7, 112.0, 105.3, 105.0, 69.8, 69.3, 62.9, 37.3, 31.5, 31.1, 27.7, 26.3, 26.0, 18.4, -5.0

IR: 2928, 2851, 1948, 1754, 1610, 1477, 1250, 1101 cm^{-1}

HRMS: (EI) calculated for [$C_{23}H_{38}O_2Si$]: 374.2641 $[M]^{+\bullet}$, found 374.2630

Ethyl (*E*)-3-methyl-4-((tetrahydro-4*H*-pyran-4-ylidene)methyl)penta-2,4-dienoate (3)

Notebook: DJL-5-183



Prepared according to general procedure **A**, 0.80 mmol scale.

Purification: column chromatography on silica gel eluting with 20% (ether : hexanes), clear colorless oil, 174 mg, 93%.

TLC: R_f = 0.26 (20% ether : hexanes), UV, I_2, vanillin stain (light blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.93 (d, *J* = 0.5 Hz, 1H), 5.81 (s, 1H), 5.57 (d, *J* = 0.5 Hz, 1H), 5.15 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.76 – 3.72 (t, *J* = 5.5 Hz, 2H), 3.63 (t, *J* = 5.8 Hz, 2H), 2.37 – 2.24 (m, 7H), 1.29 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 153.8, 145.6, 139.4, 122.3, 119.0, 118.1, 69.6, 69.0, 60.0, 37.1, 31.0, 15.5, 14.5

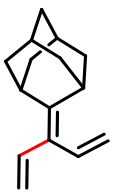
IR: 2957, 2913, 2841, 1713, 1620, 1449, 1278, 1185, 1097 cm^{-1}

HRMS: (EI) calculated for [$C_{14}H_{20}O_3$]: 236.1412 $[M]^{+\bullet}$, found 236.1415

(E:Z): > 20:1 , see spectra section

(1*R*, 3*R*)-2-(Penta-1,4-dien-3-ylidene)adamantine (4)

Notebook: DJL-4-195



Prepared according to general procedure **A**, 0.30 mmol scale.

Purification: column chromatography on silica gel eluting with 100% pentanes, clear colorless oil, 55 mg, 91%.

TLC: R_f = 0.64 (100% pentanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.52 (dd, *J* = 17.5, 11.0 Hz, 2H), 5.15 (ddd, *J* = 19.7, 14.2, 2.3 Hz, 4H), 3.12 (s, 2H), 1.96 (m, 2H), 1.92 – 1.85 (m, 6H), 1.78 (m, 4H)

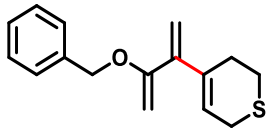
^{13}C NMR: (126 MHz, $CDCl_3$) δ 149.3, 133.9, 126.3, 116.3, 39.5, 37.3, 34.0, 28.3

IR: 3078, 2912, 2851, 1621, 1450 cm^{-1}

HRMS: (EI) calculated for [$C_{15}H_{20}$]: 200.1565 $[M]^{+\bullet}$, found 200.1564

4-(3-(Benzyloxy)buta-1,3-dien-2-yl)-3,6-dihydro-2*H*-thiopyran (5)

Notebook: DJL-6-175



Prepared according to general procedure **A**, 0.40 mmol scale.

Purification: column chromatography on silica gel eluting with 1 CV hexanes then 2% (ether : hexanes), light yellow oil, 83.6 mg, 81%.

TLC: R_f = 0.46 (7% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.45 – 7.26 (m, 5H), 6.09 – 5.81 (m, 1H), 5.44 (d, *J* = 1.5 Hz, 1H), 5.10 (d, *J* = 1.5 Hz, 1H), 4.83 (s, 2H), 4.31 (m, 2H), 3.26 (m, 2H), 2.78 (t, *J* = 5.8 Hz, 2H), 2.50 – 2.44 (m, 2H)

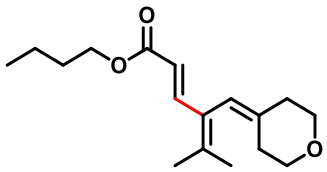
^{13}C NMR: (126 MHz, $CDCl_3$) δ 159.8, 147.9, 137.7, 137.2, 128.5, 127.8, 127.4, 123.2, 113.3, 87.0, 69.7, 28.6, 25.9, 25.3

IR: 3689, 2957, 2919, 2869, 1625, 1576, 1328, 1190 cm^{-1}

HRMS: (EI) calculated for [$C_{16}H_{18}OS$] : 258.1078 $[M]^{+\bullet}$, found 258.1083

_n_-Butyl (_E_)-5-methyl-4-((tetrahydro-4_H_-pyran-4-ylidene)methyl)hexa-2,4-dienoate (6)

Notebook: MRM-1-070



Prepared according to general procedure **B**, 0.40 mmol scale.

Purification: column chromatography on silica gel eluting with 10% then 20% (ether : hexanes), clear colorless oil, 108 mg, 97%.

TLC: R_f = 0.27 (20% ether : hexanes), UV, I_2, $KMnO_4$

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 15.3 Hz, 1H), 5.72 (d, *J* = 12.5 Hz, 1H), 5.63 (s, 1H), 4.14 (t, *J* = 6.7 Hz, 2H), 3.74 (t, 2H), 3.59 (t, *J* = 5.5 Hz, 2H), 2.35 (t, *J* = 3.6 Hz, 2H), 2.00 (t, *J* = 5.3 Hz, 2H), 1.97 (s, 3H), 1.80 (s, 3H), 1.64 (pent, *J* = 6.8 Hz, 2H), 1.44 – 1.35 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H)

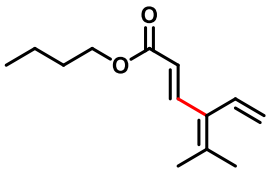
^{13}C NMR: (125 MHz, $CDCl_3$) δ 168.2, 143.1, 142.2, 139.1, 128.8, 119.7, 117.8, 69.7, 68.6, 64.2, 36.3, 31.0, 30.9, 23.6, 20.4, 19.3, 13.9

IR: 2956 (m), 2845 (w), 1710 (s), 1610 (s), 1455 (w), 1378 (w) cm^{-1}

HRMS: (EI) calculated for [$C_{17}H_{26}O_3$]: 278.1882 $[M]^{+\bullet}$, found 278.1876

_n_-Butyl (_E_)-5-methyl-4-vinylhexa-2,4-dienoate (7)

Notebook: MRM-1-069



Prepared according to general procedure **B**, 0.40 mmol scale.

Purification: column chromatography on silica gel eluting with 1 CV hexanes then 5% (ether : hexanes), slightly yellow oil, 67 mg, 86%.

TLC: R_f = 0.22 (5% ether : hexanes), UV, I_2, $KMnO_4$

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 15.7 Hz, 1H), 6.34 (dd, *J* = 17.8, 11.2 Hz, 1H), 5.87 (d, *J* = 15.7 Hz, 1H), 5.35 (m, 1H), 5.12 (m, 1H), 4.15 (t, *J* = 6.7 Hz, 2H), 1.96 (s, 3H), 1.90 (s, 3H), 1.67 – 1.61 (m, 2H), 1.45 – 1.36 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H)

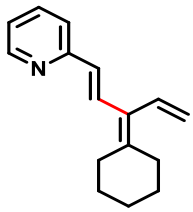
^{13}C NMR: (125 MHz, $CDCl_3$) δ 168.0, 142.1, 141.4, 133.6, 130.7, 119.2, 119.1, 64.2, 30.9, 23.0, 21.3, 19.3, 13.9

IR: 3091 (w), 2962 (w), 2928 (w), 2878 (w), 1719 (s), 1612 (m), 1460 (w), 1381 (w) cm^{-1}

HRMS: (EI) calculated for [$C_{13}H_{20}O_2$] : 208.1463 $[M]^{+\bullet}$, found 208.1461

(_E_)-2-(3-Cyclohexylidenepenta-1,4-dien-1-yl)pyridine (8)

Notebook: MRM-1-073



Prepared according to general procedure **B**, 0.40 mmol scale.

Purification: column chromatography on silica gel eluting with hexanes then 10% then 20% (ether : hexanes), pale yellow oil, 81 mg, 90%.

TLC: R_f = 0.29 (20% ether : hexanes), UV, I_2, $KMnO_4$

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.57 – 8.51 (m, 1H), 7.66 (d, *J* = 15.8 Hz, 1H), 7.59 (m, 1H), 7.28 – 7.22 (d, *J* = 8.0 Hz, 1H), 7.09 – 7.04 (m, 1H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.50 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.33 (m, 1H), 5.20 – 5.14 (m, 1H), 2.49 (t, *J* = 5.4 Hz, 2H), 2.41 (t, *J* = 5.6 Hz, 2H), 1.60 (bs, 6H)

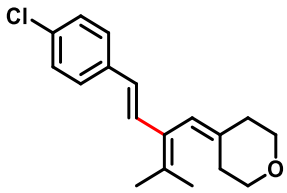
^{13}C NMR: (125 MHz, $CDCl_3$) δ 156.5, 149.6, 144.7, 136.5, 134.6, 130.4, 129.9, 129.0, 121.9, 121.6, 118.3, 32.5, 31.5, 28.6, 27.0

IR: 3078 (w), 3056 (w), 3000 (w), 2973 (w), 2923 (s), 2851 (m), 1621 (m), 1583 (s), 1560 (m) cm^{-1}

HRMS: (EI) calculated for [$C_{16}H_{19}N$]: 225.1517 $[M]^{+\bullet}$, found 225.1507

(*E*)-4-(2-(4-Chlorostyryl)-3-methylbut-2-en-1-ylidene)tetrahydro-2*H*-pyran (9)

Notebook: MRM-1-080



Prepared according to general procedure **B**, 0.40 mmol scale.

Purification: column chromatography on silica gel eluting with hexanes then 7.5% then 15% (ether : hexanes), off-white solid, 86 mg, 75%.

TLC: R_f = 0.44 (20% ether : hexanes), UV, I_2, $KMnO_4$

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 7.28 – 7.23 (m, 2H), 7.20 – 7.14 (d, *J* = 16.0 Hz, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 5.72 (s, 1H), 3.81 – 3.76 (t, *J* = 10.3 Hz, 2H), 3.62 (t, *J* = 10.3 Hz, 2H), 2.41 (t, *J* = 7.9 Hz, 2H), 2.08 (t, *J* = 8.1, 2H), 1.95 (s, 3H), 1.79 (s, 3H)

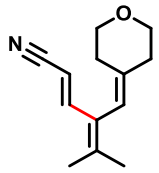
^{13}C NMR: (125 MHz, $CDCl_3$) δ 138.2, 137.0, 134.9, 132.4, 129.6, 128.8, 127.7, 127.5, 127.2, 120.9, 69.9, 68.7, 36.5, 31.1, 23.3, 20.1

IR: 2967 (w), 2901 (m), 2845 (m), 1616 (w), 1488 (m), 1234 (m), 1167 (m) cm^{-1}

HRMS: (EI) calculated for [$C_{18}H_{21}OCl$]: 288.1268 $[M]^{+\bullet}$, found 288.1271

(*E*)-5-Methyl-4-((tetrahydro-4*H*-pyran-4-ylidene)methyl)hexa-2,4-dienenitrile (10)

Notebook: MRM-1-072



Prepared according to general procedure **B**, 0.40 mmol scale.

Purification: column chromatography on silica gel eluting with 40% (ether : hexanes), colorless oil, 66 mg, 81%.

TLC: R_f = 0.32 (40 % ether : hexanes), UV, I_2, $KMnO_4$

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 16.0 Hz, 1H), 5.56 (s, 1H), 5.20 (d, *J* = 16.0 Hz, 1H), 3.71 (t, *J* = 5.5 Hz, 2H), 3.58 (t, *J* = 5.5 Hz, 2H), 2.34 (t, *J* = 5.4 Hz, 2H), 1.98 (t, *J* = 5.5 Hz, 2H), 1.94 (s, 3H), 1.81 (s, 3H)

^{13}C NMR: (125 MHz, $CDCl_3$) δ 147.7, 144.5, 140.9, 128.7, 119.5, 118.0, 95.1, 69.6, 68.5, 36.3, 31.0, 23.7, 20.3

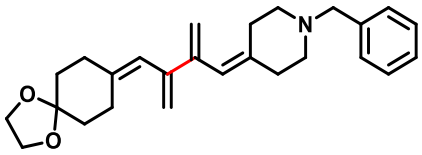
IR: 2956 (w), 2912 (w), 2845 (w), 2214 (m), 1660 (w), 1610 (m), 1588 (m), 1101 (s) cm^{-1}

HRMS: (EI) calculated for [$C_{13}H_{17}NO$] : 203.1310 [M]$^{+\bullet}$, found 203.1301

(*E*:*Z*) : (*E*)- major , ~ (7.5 : 1) ratio

4-(3-((1,4-Dioxaspiro[4.5]decan-8-ylidene)methyl)-2-methylenebut-3-en-1-ylidene)-1-benzylpiperidine (11)

Notebook: DJL-4-235



Prepared according to general procedure **C**, 0.30 mmol scale.

Purification: column chromatography on silica gel eluting with 25% then 40% (ether : hexanes), colorless oil, 95 mg, 81%.

TLC: R_f = 0.33 (40% ether : hexanes), UV, I_2, vanillin stain (olive green spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.32 (m, 4H), 7.24 (m, 1H), 5.82 (d, *J* = 9.5 Hz, 2H), 5.23 (d, *J* = 8.0 Hz, 2H), 4.91 (s, 2H), 3.97 (s, 4H), 3.50 (s, 2H), 2.52 – 2.46 (m, 2H), 2.44 – 2.39 (m, 2H), 2.38 – 2.30 (m, 8H), 1.77 – 1.73 (t, *J* = 6.5 Hz, 2H), 1.67 – 1.63 (t, *J* = 6.3 Hz, 2H)

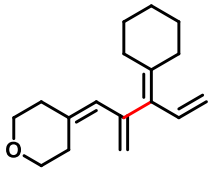
^{13}C NMR: (126 MHz, $CDCl_3$) δ 145.0, 144.6, 140.7, 140.2, 138.7, 129.2, 128.3, 127.0, 122.7, 122.2, 115.9, 115.8, 108.9, 64.4, 63.2, 55.4, 54.9, 36.4, 36.3, 35.8, 33.8, 29.6, 26.4

IR: 3095, 3029, 2945, 2879, 2795, 1583, 1450, 1356, 1267 cm^{-1}

HRMS: (EI) calculated for [$C_{26}H_{33}NO_2$]: 391.2511 [M]$^{+\bullet}$, found 391.2500

4-(3-Cyclohexylidene-2-methylenepent-4-en-1-ylidene)tetrahydro-2*H*-pyran (12)

Notebook: DJL-5-149



Prepared according to general procedure **C**, 0.50 mmol scale.

Purification: column chromatography on silica gel eluting with 2% then 5% (ether : hexanes), colorless oil, 51 mg, 42%.

TLC: R_f = 0.32 (5% ether : hexanes), UV, I_2, vanillin stain (violet spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.83 (d, *J* = 0.5 Hz, 1H), 5.20 (d, *J* = 2.5 Hz, 1H), 5.11 – 5.01 (m, 2H), 4.81 – 4.75 (d, *J* = 3.0 Hz, 1H), 3.73 – 3.66 (t, *J* = 5.5 Hz, 2H), 3.62 – 3.51 (t, *J* = 5.5 Hz, 2H), 2.50 – 2.41 (m, 2H), 2.37 – 2.30 (m, 2H), 2.27 – 2.20 (m, 2H), 2.20 – 2.09 (t, *J* = 6.0 Hz, 2H), 1.62 – 1.54 (m, 4H), 1.53 – 1.43 (m, 2H)

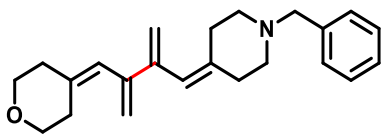
^{13}C NMR: (126 MHz, $CDCl_3$) δ 144.0, 139.9, 136.5, 133.2, 132.7, 125.4, 118.9, 114.9, 69.8, 68.9, 38.3, 33.2, 30.5, 29.9, 28.3, 28.1, 27.0

IR: 3089, 2928, 2851, 1632, 1444, 1228 cm^{-1}

HRMS: (EI) calculated for [$C_{17}H_{24}O$]: 244.1827 $[M]^{+\bullet}$, found 244.1821

1-Benzyl-4-(2-methylene-3-((tetrahydro-4*H*-pyran-4-ylidene)methyl)but-3-en-1-ylidene)piperidine (13)

Notebook: DJL-5-148



Prepared according to general procedure **C**, 0.50 mmol scale.

Purification: column chromatography on silica gel eluting with 20% then 40% (ether : hexanes), light yellow oil, 110 mg, 66%.

TLC: R_f =0.27 (40% ether : hexanes), UV, I_2, vanillin (grey spot)

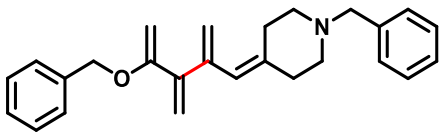
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 4H), 7.25 (m, 1H), 5.86 (s, 1H), 5.80 (s, 1H), 5.25 (dd, *J* 8.8, 1.8 Hz, 2H), 4.95 – 4.90 (bt, *J* = 1.0 Hz, 2H), 3.76 – 3.71 (t, *J* = 5.5 Hz, 2H), 3.64 (t, *J* = 5.5 Hz, 2H), 3.51 (s, 2H), 2.48 (t, *J* = Hz, 2H), 2.40 (m, 2H), 2.38 – 2.33 (m, 4H), 2.33 – 2.30 (m, 4H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 144.6, 144.4, 140.4, 138.7, 138.2, 129.2, 128.3, 127.1, 123.0, 122.1, 116.1, 116.0, 69.7, 69.1, 63.2, 55.4, 54.9, 37.2, 36.3, 31.1, 29.6

IR: 3095, 3029, 2963, 2908, 2847, 2797, 1719, 1587, 1289, 1234 cm^{-1}

1-Benzyl-4-(4-(benzyloxy)-2,3-dimethylenepent-4-en-1-ylidene)piperidine (14)

Notebook: DJL-4-259



Prepared according to general procedure **C**, 0.30 mmol scale.

Purification: column chromatography on silica gel eluting with 20% then 40% (ether : hexanes), clear light yellow oil, 65 mg, 58%.

TLC: R_f = 0.34 (40% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 3H), 7.36 – 7.31 (m, 6H), 7.30 – 7.24 (m, 1H), 5.84 (s, 1H), 5.55 (s, 1H), 5.26 – 5.21 (s, 1H), 5.17 (s, 1H), 5.10 – 5.06 (s, 1H), 4.85 (s, 2H),

4.39 (s, 1H), 4.32 (s, 1H), 3.51 (s, 2H), 2.48 (m, 2H), 2.47 – 2.44 (m, 2H), 2.39 (m, 2H), 2.29 (t, *J* = 5.5 Hz, 2H)

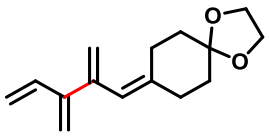
^{13}C NMR: (126 MHz, $CDCl_3$) δ 159.3, 146.6, 144.5, 140.1, 138.7, 137.4, 129.2, 128.5, 128.3, 128.3, 127.8, 127.4, 127.1, 123.4, 118.1, 114.9, 87.5, 69.7, 63.1, 55.3, 54.6, 36.9, 29.4

IR: 3034, 2945, 2901, 2795, 2757, 1732, 1588, 1455 cm^{-1}

HRMS: (EI) calculated for [$C_{26}H_{28}NO$]: 370.2171 $[M-H]^+$, found 370.2169

8-(2,3-Dimethylenepent-4-en-1-ylidene)-1,4-dioxaspiro[4.5]decane (15)

Notebook: DJL-5-089, DJL-6-095



Prepared according to general procedure **C**, 0.267 mmol scale.

Purification: column chromatography on silica gel eluting with 10% (ether : hexanes), colorless oil, 42.5 mg, 68%.

TLC: R_f = 0.35 (20% ether : hexanes), UV, I_2, vanillin stain (olive green spot)

^{1}H NMR: (600 MHz, $CDCl_3$) δ 6.65 – 6.38 (dd, *J* = 17.4, 10.2 Hz, 1H), 5.85 – 5.80 (s, 1H), 5.33 (m, 1H), 5.21 – 5.10 (m, 3H), 5.09 – 5.01 (m, 2H), 3.96 (s, 4H), 2.43 – 2.40 (t, *J* = 6.6 Hz, 2H), 2.31 (t, *J* = 6.3 Hz, 2H), 1.74 – 1.71 (t, *J* = 6.6 Hz, 2H), 1.65 – 1.62 (t, *J* = 6.6 Hz, 2H)

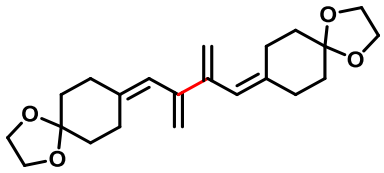
^{13}C NMR: (151 MHz, $CDCl_3$) δ 148.5, 144.4, 140.6, 137.2, 123.6, 116.8, 116.7, 115.6, 108.9, 64.5, 36.3, 35.5, 34.3, 26.1

IR: 3089, 2946, 2875, 2847, 1581, 1432, 1267 cm^{-1}

HRMS: (EI) calculated for [$C_{15}H_{21}O_2$]: 233.1542 $[M+H]^+$, found 233.1546

8,8'-(2,3-Dimethylenebutane-1,4-diylidene)bis(1,4-dioxaspiro[4.5]decane) (16)

Notebook: DJL-4-227/289



Prepared according to general procedure **D**, 0.25 mmol scale.

Purification: column chromatography on silica gel eluting with 20% then 40% (ether : hexanes), white crystalline solid, 56 mg, 63%.

TLC: R_f = 0.40 (40% ether : hexanes), UV, I_2, vanillin stain (Forrest green spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.83 (s, 1H), 5.22 (s, 1H), 4.90 (s, 1H), 3.96 (s, 4H), 2.34 (q, *J* = 6.3 Hz, 8H), 1.76 – 1.72 (t, *J* = 6.5 Hz 4H), 1.66 – 1.62 (t, *J* = 6.5 Hz, 4H)

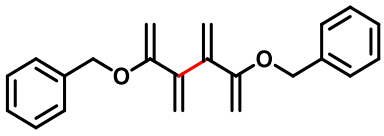
^{13}C NMR: (126 MHz, $CDCl_3$) δ 144.9, 140.8, 122.6, 115.8, 109.0, 64.5, 36.4, 35.8, 33.8, 26.4

IR: 2945, 2890, 1716, 1439, 1239, 1123 cm^{-1}

HRMS: (EI) calculated for [$C_{22}H_{30}O_4$]: 358.2144 $[M]^{+\bullet}$, found 358.2139

(((3,4-Dimethylenehexa-1,5-diene-2,5-diyl)bis(oxy))bis(methylene))dibenzene (17)

Notebook: DJL-4-255, DJL-6-096



Prepared according to general procedure **D**, 0.25 mmol scale.

Purification: column chromatography on silica gel eluting with pentanes then 3% (ether : hexanes), viscous clear light yellow oil, 63 mg, 79%.

TLC: R_f = 0.54 (10% ether : hexanes), UV, I_2 (strong)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.49 – 7.35 (m, 8H), 7.36 – 7.31 (m, 2H), 5.80 (s, 2H), 5.21 (s, 2H), 4.87 (s, 4H), 4.46 (s, 2H), 4.32 – 4.29 (s, 2H)

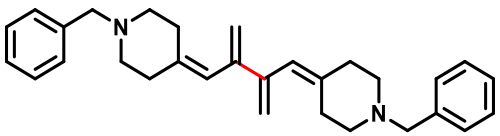
^{13}C NMR: (126 MHz, $CDCl_3$) δ 159.0, 143.8, 137.4, 128.6, 127.8, 127.4, 116.2, 87.1, 69.7

IR: 3073, 3034, 2924, 2863, 1724, 1570, 1460, 1289, 1124 cm^{-1}

HRMS: (EI) calculated for $[C_{22}H_{22}O_2]$: 318.1620 $[M]^{+\bullet}$, found 318.1616

4,4'-(2,3-Dimethylenebutane-1,4-diylidene)bis(1-benzylpiperidine) (18)

Notebook: DJL-5-002



Prepared according to general procedure **D**, 0.4875 mmol scale.

Purification: column chromatography on silica gel eluting with 30% (ether : DCM), viscous bronze oil, 157 mg, 76%.

TLC: R_f = 0.42 (50% ether : DCM), UV, I_2, vanillin stain (crimson spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 8H), 7.25 (m, 2H), 5.80 (s, 2H), 5.23 (d, *J* = 2.0 Hz, 2H), 4.91 (s, 2H), 3.52 (s, 4H), 2.52 – 2.48 (t, *J* = 5.5 Hz, 4H), 2.40 (t, *J* = 5.3 Hz, 4H), 2.37 – 2.33 (t, *J* = 5.3 Hz, 4H), 2.31 (t, *J* = 5.5 Hz, 4H)

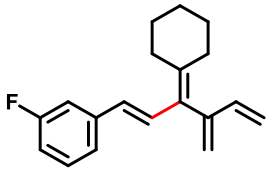
^{13}C NMR: (126 MHz, $CDCl_3$) δ 144.7, 140.1, 138.7, 129.3, 128.3, 127.1, 122.3, 115.9, 63.2, 55.4, 54.9, 36.3, 29.6

IR: 3084 (w), 3023 (w), 2941 (m), 2897 (m), 2797 (m), 2764 (m), 1818 (w), 1713 (m) cm^{-1}

HRMS: (EI) calculated for $[C_{30}H_{36}N_2]$: 424.2878 $[M]^{+\bullet}$, found 424.2862

(*E*)-1-(3-Cyclohexylidene-4-methylenehexa-1,5-dien-1-yl)-3-fluorobenzene (20)

Notebook: RTHL-7-151-A



Prepared according to general procedure **A**, 0.30 mmol scale.

Purification: column chromatography on silica gel eluting with hexanes then 2% (ether : hexanes), colorless oil, 66 mg, 82%.

TLC: R_f = 0.54 (3% ether : hexanes), UV, I_2

^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 1H), 7.23 (m, 1H), 7.13 (m, 1H), 7.09 (m, 1H), 6.95 – 6.76 (m, 1H), 6.55 – 6.40 (dd, *J* = 17.1, 10.5 Hz, 1H), 6.34 (d, *J* = 15.6 Hz, 1H), 5.40 (s, 1H), 5.12 – 5.04 (m, 2H), 4.98 (s, 1H), 2.57 – 2.49 (t, *J* = 5.7 Hz, 2H), 2.18 – 2.13 (t, *J* = 6.0 Hz, 2H), 1.69 – 1.59 (m, 4H), 1.52 (m, 2H)

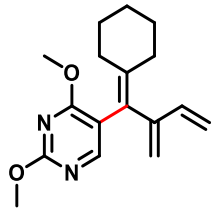
^{13}C NMR: (151 MHz, $CDCl_3$) δ 164.1, 162.5, 146.4, 143.5, (141.1, 141.0, d, *J* = 7.9 Hz), 138.1, (130.0, 129.9, d, *J* = 8.5 Hz), 129.0, (127.9, 127.9, d, *J* = 2.7 Hz), 126.9, (122.3, 122.2, d, *J* = 2.7 Hz), 118.8, (116.1, 116.1, d, *J* = 4.1 Hz), (113.7, 113.5, 112.6, 112.4, dd, *J* = 166.4, 21.6 Hz), 33.6, 30.3, 28.8, 28.8, 27.0

IR: 3089, 3041, 2924, 2853, 1603, 1579, 1484, 1444, 1384, 1351, 1301, 1268, 1240, 1164, 1143, 1073, 1037, 986, 964, 951, 900, 867, 852, 816, 774, 726, 703, 681, 622, 561, 519 cm^{-1}

HRMS: (EI) calculated for $[C_{19}H_{21}F]$: 268.1627 $[M]^{+\bullet}$, found 268.1625

5-(1-Cyclohexylidene-2-methylenebut-3-en-1-yl)-2,4-dimethoxypyrimidine (21)

Notebook: RTHL-7-155



Prepared according to general procedure **A**, 0.30 mmol scale.

Purification: column chromatography on silica gel eluting with 8% then 15% (ether : hexanes), colorless oil, 81 mg, 94%.

TLC: R_f = 0.35 (10% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.06 – 7.95 (s, 1H), 6.31 (dd, *J* = 17.3, 10.3 Hz, 1H), 5.30 (d, *J* = 17.5, 1.0 Hz, 1H), 5.18 – 5.06 (m, 2H), 5.03 (d, *J* = 10.5 Hz, 1H), 3.95 (d, *J* = 3.0 Hz, 6H), 2.16 (m, 2H), 1.94 (m, 2H), 1.54 (m, 6H)

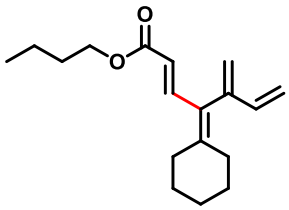
^{13}C NMR: (126 MHz, $CDCl_3$) δ 168.4, 164.2, 156.0, 148.2, 143.6, 138.0, 121.0, 118.0, 116.1, 115.9, 54.7, 53.8, 32.3, 32.1, 28.6, 28.1, 26.7

IR: 3100, 2925, 2853, 1588, 1553, 1465, 1393, 1377, 1335, 1315, 1284, 1271, 1256, 1231, 1199, 1134, 1077, 1017, 988, 975, 899, 873, 853, 818, 797, 766, 740, 724, 675, 637, 600, 561, 460 cm^{-1}

HRMS: (EI) calculated for [$C_{17}H_{22}N_2O_2$]: 286.1681 $[M]^{+\bullet}$, found 286.1674

_n_-Butyl (_E_)-4-cyclohexylidene-5-methylenehepta-2,6-dienoate (22)

Notebook: DJL-5-280



Prepared according to general procedure **B**, 1.50 mmol scale.

Purification: column chromatography on silica gel eluting with hexanes then 2% (ether : hexanes), colorless oil, 259.1 mg, 63%.

TLC: R_f = 0.15 (2% ether : hexanes), UV, I_2, vanillin stain (purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.88 (ABq, J_{AB} = 15.5 Hz, 1H), 6.46 – 6.39 (dd, J = 17.3, 10.3 Hz, 1H), 5.71 (ABq, J_{AB} = 15.0 Hz, 1H), 5.34 (s, 1H), 5.04 – 4.97 (m, 2H), 4.92 (s, 1H), 4.11 (t, J = 6.8 Hz, 2H), 2.56 – 2.49 (t, J = 6.0 Hz, 2H), 2.16 – 2.12 (t, J = 6.0 Hz, 2H), 1.66 – 1.57 (m, 6H), 1.51 (m, 2H), 1.41 – 1.36 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H)

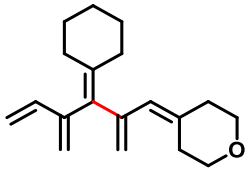
^{13}C NMR: (126 MHz, $CDCl_3$) δ 168.4, 151.2, 145.4, 140.9, 137.7, 128.2, 119.1, 118.6, 116.2, 64.2, 33.9, 31.0, 30.6, 28.8, 28.8, 26.8, 19.3, 13.9

IR: 3084, 2963, 2935, 2858, 1702, 1609, 1289 cm^{-1}

HRMS: (EI) calculated for [$C_{18}H_{26}O_2$]: 274.1933 $[M]^{+\bullet}$, found 274.1931

4-(3-Cyclohexylidene-2,4-dimethylenehex-5-en-1-ylidene)tetrahydro-2*H*-pyran (23)

Notebook: DJL-5-223



Prepared according to general procedure **C**, 0.50 mmol scale.

Purification: column chromatography on silica gel eluting with 5% (ether : hexanes), clear colorless oil, 100 mg, 74%.

TLC: R_f = 0.24 (7% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.35 (dd, *J* = 17.0, 10.5 Hz, 1H), 5.67 (d, *J* = 0.5 Hz, 1H), 5.24 – 5.19 (dd, *J* = 17.3, 1.8 Hz, 1H), 5.14 (d, *J* = 2.0 Hz, 1H), 5.09 – 5.05 (d, *J* = 10.5 Hz, 1H), 5.00 (d, *J* = 2.5 Hz, 1H), 4.95 – 4.90 (m, 2H), 3.69 (t, *J* = 5.5 Hz, 2H), 3.63 – 3.58 (t, *J* = 5.5 Hz, 2H), 2.46 (td, *J* = 5.7, 2.8 Hz, 2H), 2.35 – 2.28 (m, 2H), 2.25 – 2.21 (m, 2H), 2.07 – 2.00 (t, *J* = 6.0 Hz, 2H), 1.59 – 1.53 (m, 4H), 1.51 – 1.44 (m, 2H)

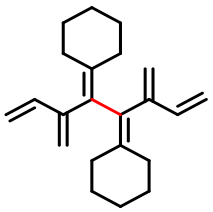
^{13}C NMR: (126 MHz, $CDCl_3$) δ 147.8, 144.8, 139.1, 138.3, 136.5, 131.0, 125.1, 117.3, 116.4, 116.0, 69.7, 69.1, 37.5, 32.5, 31.7, 31.0, 28.8, 28.6, 26.9

IR: 3084, 2957, 2930, 2841, 1587, 1449 cm^{-1}

HRMS: (EI) calculated for [$C_{19}H_{26}O$]: 270.1984 $[M]^{+\bullet}$, found 270.1986

(3,6-Dimethyleneocta-1,7-diene-4,5-diylidene)dicyclohexane (24)

Notebook: RTHL-7-153



***Note:** For purely hydrocarbon products an additional 3-6 inches of silica gel is used, relative to a 'typical' column length. This helps to increase separation from any trace impurities since for these compounds' columns are run by eluting with pure pentanes.

Prepared according to general procedure **D**, 0.30 mmol scale.

Purification: column chromatography on silica gel eluting with 100% pentanes, colorless oil, 24 mg, 27%.

TLC: R_f = 0.58 (100% hexanes), UV, I_2

^{1}H NMR: (600 MHz, $CDCl_3$) δ 6.32 – 6.25 (dd, *J* = 17.4, 10.2 Hz, 2H), 5.12 (d, *J* = 17.4 Hz, 2H), 5.07 (s, 2H), 4.97 (d, *J* = 10.8 Hz, 2H), 4.83 (s, 2H), 2.38 (m, 2H), 2.20 – 1.96 (m, 6H), 1.54 (m, 12H)

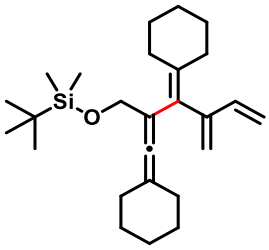
^{13}C NMR: (151 MHz, $CDCl_3$) δ 148.4, 138.9, 137.3, 129.7, 117.4, 115.5, 32.3, 31.9, 28.2, 27.8, 26.9

IR: 3087, 3011, 2921, 2851, 1613, 1582, 1446, 1379, 1263, 1228, 1108, 1033, 980, 889, 853, 802, 753, 735, 528, 466 cm^{-1}

HRMS: (EI) calculated for [$C_{22}H_{30}$]: 294.2348 $[M]^{+\bullet}$, found 294.2352

***tert*-Butyl((3-cyclohexylidene-2-(cyclohexylidenemethylene)-4-methylenehex-5-en-1-yl)oxy)dimethylsilane (25)**

Notebook: DJL-6-035-B



Prepared according to general procedure **A**, 0.30 mmol scale.

Purification: column chromatography on silica gel eluting with 1 CV hexanes then 1% (ether : hexanes), colorless oil, 70 mg, 58%.

TLC: R_f = 0.76 (20% ether : hexanes), UV, I_2, vanillin stain (forest green spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.43 – 6.30 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.22 (m, 1H), 5.15 (m, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 4.96 (bs, 1H), 4.02 (s, 2H), 2.32 (m, 2H), 2.15 – 2.03 (m, 6H), 1.68 – 1.59 (m, 2H), 1.57 – 1.45 (m, 10H), 0.87 (s, 9H), 0.01 (s, 6H)

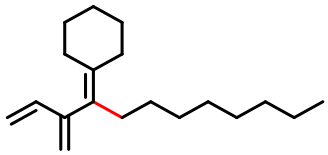
^{13}C NMR: (126 MHz, $CDCl_3$) δ 196.7, 147.3, 140.2, 138.1, 125.8, 117.3, 116.5, 102.5, 102.0, 63.3, 32.4, 31.8, 31.2, 28.9, 28.9, 27.5, 27.1, 26.4, 26.1, 18.5, -5.1

IR: 2924, 2852, 1785, 1587, 1449, 1256, 1080 cm^{-1}

HRMS: (EI) calculated for [$C_{26}H_{42}OSi$]: 398.3005 $[M]^{+\bullet}$, found 398.2996

(3-Methylenedodec-1-en-4-ylidene)cyclohexane (26)

Notebook: DJL-6-004-B



***Note:** Reactions indicated full conversion of the starting allenoate into a single product, *via* TLC; thus, the decreased yield is most likely due to its high volatility.

Prepared according to general procedure **A**, 0.40 mmol scale.

Purification: column chromatography on silica gel eluting with 100% pentanes, colorless oil, 43 mg, 41%.

TLC: R_f = 0.70 (3% ether : hexanes), UV, I_2, vanillin stain (light blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.42 – 6.31 (dd, *J* = 17.3, 10.3 Hz, 1H), 5.13 – 5.06 (m, 2H), 5.03 (d, *J* = 10.3 Hz, 1H), 4.84 – 4.78 (bs, 1H), 2.24 – 2.20 (m, 2H), 2.08 – 2.04 (t, *J* = 7.5 Hz, 2H), 2.01 – 1.96 (t, *J* = 6.0 Hz, 2H), 1.58 – 1.54 (m, 4H), 1.45 – 1.41 (m, 2H), 1.31 – 1.24 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H)

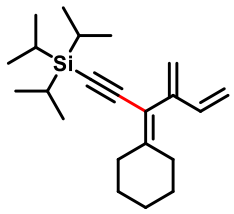
^{13}C NMR: (126 MHz, $CDCl_3$) δ 149.7, 138.6, 136.1, 129.1, 116.1, 115.4, 32.5, 32.1, 32.1, 30.1, 29.9, 29.7, 29.5, 29.3, 28.8, 28.7, 27.1, 22.8, 14.3

IR: 2923, 2862, 1716, 1450, 1056 cm^{-1}

HRMS: (EI) calculated for [$C_{19}H_{32}$]: 260.2504 $[M]^{+\bullet}$, found 260.2500

(3-Cyclohexylidene-4-methylenehex-5-en-1-yn-1-yl)triisopropylsilane (27)

Notebook: DJL-5-299-A



Prepared according to general procedure **A**, 0.30 mmol scale.

Purification: column chromatography on silica gel eluting with 100% pentanes, colorless oil, 82 mg, 83%.

TLC: R_f = 0.61 (100% hexanes), UV, I_2, vanillin stain (purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.37 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.34 – 5.27 (m, 1H), 5.19 (d, *J* = 1.5 Hz, 1H), 5.12 (d, *J* = 10.5 Hz, 1H), 5.03 (s, 1H), 2.62 – 2.58 (t, *J* = 6.0 Hz, 2H), 2.16 – 2.12 (t, *J* = 6.0 Hz, 2H), 1.65 (m, 2H), 1.59 – 1.54 (m, 2H), 1.49 (m, 2H), 1.08 – 1.06 (m, 21H)

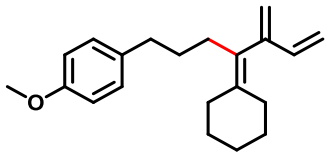
^{13}C NMR: (126 MHz, $CDCl_3$) δ 152.2, 145.5, 137.2, 117.8, 116.5, 113.6, 106.8, 92.5, 33.6, 31.5, 28.5, 28.2, 26.7, 18.8, 11.6

IR: 2930, 2863, 2137, 2065, 1587, 1466, 1003 cm^{-1}

HRMS: (EI) calculated for [$C_{22}H_{36}Si$]: 328.2586 $[M]^{+\bullet}$, found 328.2576

1-(4-Cyclohexylidene-5-methylenehept-6-en-1-yl)-4-methoxybenzene (28)

Notebook: DJL-6-001-A



Prepared according to general procedure **A**, 0.40 mmol scale.

Purification: column chromatography on silica gel eluting with hexanes then 2% (ether : hexanes), colorless oil, 74 mg, 62%.

TLC: R_f = 0.60 (10% ether : hexanes), UV, I_2, vanillin stain (light blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.13 – 7.09 (m, 2H), 6.84 – 6.81 (m, 2H), 6.51 – 5.87 (dd, *J* = 18.0, 10.5 Hz, 1H), 5.21 – 5.08 (m, 2H), 5.05 – 5.03 (d, *J* = 10.5 Hz, 1H), 4.97 – 4.75 (s, 1H), 3.79 (s, 3H), 2.58 – 2.51 (t, *J* = 7.8 Hz, 2H), 2.24 – 2.17 (t, *J* = 5.5 Hz, 2H), 2.17 – 2.06 (t, *J* = 7.8 Hz, 2H), 2.02 (t, *J* = 6.0 Hz, 2H), 1.63 – 1.60 (m, 2H), 1.55 – 1.54 (m, 4H), 1.43 (m, 2H)

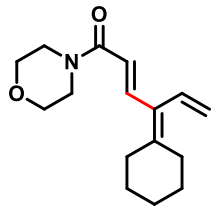
^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.9, 149.6, 138.6, 136.7, 135.2, 129.4, 128.7, 116.4, 115.7, 113.9, 55.5, 35.3, 32.6, 31.9, 31.4, 30.2, 28.9, 28.8, 27.2

IR: 2928, 2851, 1721, 1616, 1516, 1444, 1306, 1250 cm^{-1}

HRMS: (EI) calculated for [$C_{21}H_{28}O$]: 296.2140 $[M]^{+\bullet}$, found 296.2141

(*E*)-4-Cyclohexylidene-1-morpholinohexa-2,5-dien-1-one (29)

Notebook: MRM-1-048-A



Prepared according to general procedure **B**, 0.50 mmol scale.

Purification: column chromatography on silica gel eluting with 100% ether, off white solid, 87 mg, 67%.

TLC: R_f = 0.31 (100% ether), UV, I_2, $KMnO_4$

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.77 (q_{AB}, J_{AB} = 15.1 Hz, 1H), 6.35 (dd, J = 17.7, 11.1 Hz, 1H), 6.24 (q_{AB}, J_{AB} = 15.1 Hz, 1H), 5.32 (m, 1H), 5.09 (m, 1H), 3.68 (bs, 6H), 3.53 (bs, 2H), 2.44 (m, 2H), 2.39 – 2.32 (m, 2H), 1.57 (bs, 6H)

^{13}C NMR: (125 MHz, $CDCl_3$) δ 166.5, 148.7, 140.5, 134.1, 128.2, 119.0, 117.9, 67.0, 46.2, 42.5, 32.8, 31.4, 28.6, 28.6, 26.8

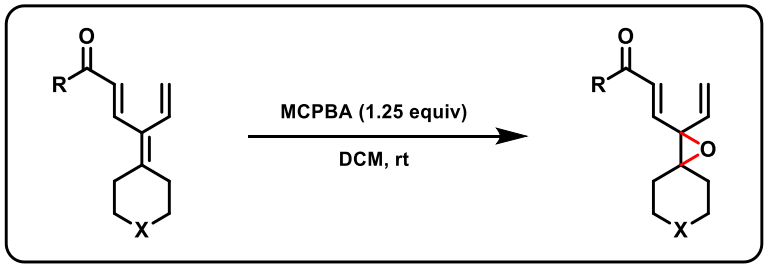
IR: 3435, 3086, 2968, 2923, 2855, 1719, 1634, 1589, 1437 cm^{-1}

HRMS: (EI) calculated for [$C_{16}H_{23}NO_2$]: 261.1729 $[M]^{+\bullet}$, found 261.1720

3. Regioselective Reactions of Dendralenes

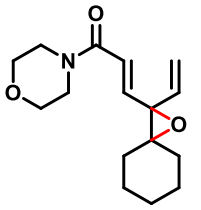
3.1 Regioselective epoxidations

3.1.1 MCPBA "electrophilic" epoxidation: General procedure



(*E*)-1-Morpholino-3-(2-vinyl-1-oxaspiro[2.5]octan-2-yl)prop-2-en-1-one (30)

Notebook: DJL-5-172



To a clean and dry RBF, under argon, was added the [3]dendralene (0.268 mmol), which was subsequently diluted with dry DCM, ~[0.10 M], and then the solution cooled to 0 ^{o}C with stirring. Once at 0 ^{o}C, MCPBA (≤ 77% pure, 1.25 molar equiv) was added, in one portion, and the reaction was allowed to stir for ~1-3 h. Upon complete consumption of starting material, *via* TLC analysis (see below), the reaction mixture was diluted with DCM and saturated aqueous $NaHSO_3$/$Na_2S_2O_5$. Subsequent transfer to a separatory funnel and extraction with DCM (x 3), followed by a washing of the collected organic extracts with DI water, drying of the resulting organic layers over anhydrous Na_2SO_4, salt filtration and rotary evaporation

afforded the crude product. Purification by silica gel column chromatography eluting with 60% (ether : DCM) afforded the title compound as a faint yellow oil, 49 mg, 66%.

***Note:** Full conversion of starting material is typically observed, *via* TLC, within 1 h. However, if full conversion is not observed, simple addition of more MCPBA to the reaction promotes further product formation and eventual complete conversion.

TLC: R_f = 0.39 (60% ether : DCM), UV, I_2 (very close R_f value, relative to S.M. R_f = 0.41)

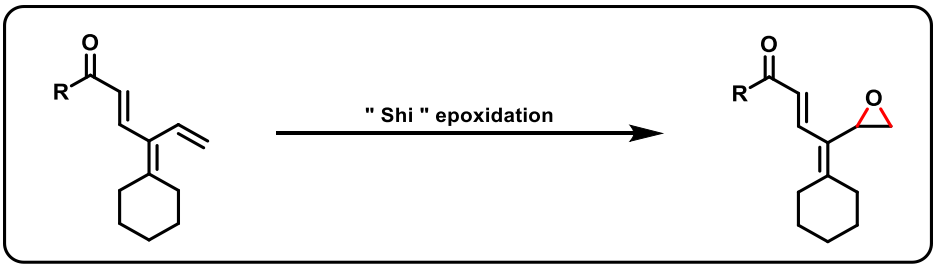
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.12 (ABq, J_{AB} = 15.0 Hz, 1H), 6.41 (ABq, J_{AB} = 15.0 Hz, 1H), 6.00 – 5.93 (m, 1H), 5.34 (d, J = 1.0 Hz, 1H), 5.32 – 5.27 (m, 1H), 3.72 – 3.61 (m, 6H), 3.53 (m, 2H), 1.70 – 1.59 (m, 4H), 1.56 – 1.48 (m, 3H), 1.45 – 1.38 (m, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 164.9, 142.1, 133.4, 121.3, 118.9, 71.6, 68.3, 66.9, 66.8, 30.4, 30.3, 25.6, 25.2, 25.0

IR: 2930, 2858, 1724, 1658, 1620, 1427 cm^{-1}

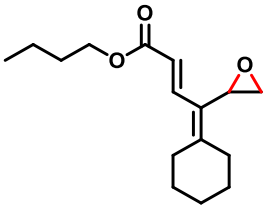
HRMS: (EI) calculated for [$C_{16}H_{23}NO_3$]: 277.1678 $[M]^{+\bullet}$, found 277.1674

3.1.2 Shi epoxidation [17] : General procedure



***n*-Butyl (*E*)-4-cyclohexylidene-4-(oxiran-2-yl)but-2-enoate**

Notebook: DJL-5-279-II



To a clean and dry RBF, charged with a stir bar, were sequentially added an aqueous solution of [0.05 M] $Na_2B_4O_7 \bullet 10H_2O$, in [4 x 10^{-4} M] Na_2EDTA ([0.10 M] relative to the reaction), DMM ([0.10 M] relative to the reaction) and acetonitrile ([0.20 M] relative to the reaction); arriving at a 1:1:2 volumetric ratio of Shi's cocktail. This mixture was then brought to 0 ^oC, with a NaCl/ice/water bath. Once cooled, the olefin (1.00 equiv, 0.464 mmol), catalytic tetrabutylammonium hydrogen sulfate (~ 4 mol %) and Shi's catalyst (fructose derived ketone, 30 mol %) were added. Upon stirring this mixture for ~5-10 min, a [0.20 M] solution of Oxone® in aqueous in [4 x 10^{-4} M] Na_2EDTA (1.25 equiv) and a [0.80 M] solution of K_2CO_3 (4.00 equiv) in DI water were added dropwise, *via* two separates syringes, over the course of 1 h. Reaction progress was checked *via* TLC analysis which indicated product formation but an incomplete reaction (see **Note** and TLC conditions below). The reaction was eventually quenched by addition of hexanes and transferred to a separatory funnel where it was extracted

with ether (x 3), dried over anhydrous Na_2SO_4, filtered from salts, and concentrated by rotary evaporation. Purification by column chromatography on silica gel, eluting with 10% then 20% (ether : hexanes), afforded the title compound as a clear colorless oil, 27 mg, 22% isolated; 66% based on recovered starting material (brsm).

***Note:** Even with additional Oxone®, more catalyst, more tetrabutylammonium hydrogen sulfate or more K_2CO_3 the reaction eventually stopped; however, even with all of these systematic adjustments no by-products were ever observed.

TLC: R_f = 0.18 (10% ether : hexanes), UV, I_2, vanillin stain (grey/blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.73 (ABq, J_{AB} = 16.0 Hz, 1H), 6.10 (ABq, J_{AB} = 15.5 Hz, 1H), 4.19 – 4.12 (m, 2H), 3.54 (t, J = 3.0 Hz, 1H), 3.06 (m, 1H), 2.62 (m 1H), 2.50 – 2.40 (m, 4H), 1.63 (m, 8H), 1.43 – 1.38 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H)

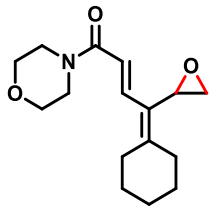
^{13}C NMR: (126 MHz, $CDCl_3$) δ 168.0, 154.7, 140.0, 124.6, 117.7, 64.3, 49.6, 48.7, 32.8, 31.2, 31.0, 28.5, 28.5, 26.6, 19.3, 13.9

IR: 3056, 2963, 2930, 2858, 1708, 1614, 1455 cm^{-1}

HRMS: (EI) calculated for [$C_{16}H_{24}O_3$]: 264.1725 $[M]^{+\bullet}$, found 264.1720

(*E*)-4-Cyclohexylidene-1-morpholino-4-(oxiran-2-yl)but-2-en-1-one (31)

Notebook: DJL-6-072



***Note:** The following adjustments were made relative to the procedure above. Exclusion of DMM as a solvent component, fructose derived ketone (1.25 equiv), Oxone® (4.00 equiv), K_2CO_3 (10.00 equiv).

Prepared according to general procedure **3.1.2**, 0.34 mmol scale.

Purification: column chromatography on silica gel eluting with 100% ether, then 100% EtOAc, clear colorless oil which co-crystallizes with an equivalent of H_2O over time into a white colorless solid, 65 mg, 69-76%.

TLC: R_f =0.20 (100% ether), UV, I_2, vanillin (grey spot)

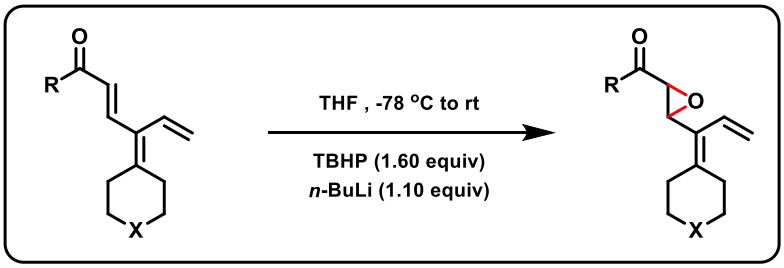
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.74 (ABq, J_{AB} = 15.0 Hz, 1H), 6.60 (ABq, J_{AB} = 15.0 Hz, 1H), 3.73 – 3.60 (m, 8H), 3.57 (t, J = 3.3 Hz, 1H), 3.07 (dd, J = 5.5, 4.0 Hz, 1H), 2.69 – 2.66 (dd, J = 5.8, 2.8 Hz, 1H), 2.43 (m, 4H), 1.61 (bs, 6H), 1.56 (s, 2H, H_2O)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 166.6, 152.8, 138.5, 124.7, 116.3, 67.1, 67.1, 50.0, 48.9, 32.6, 31.1, 28.5, 28.4, 26.6

IR: 2968, 2930, 2852, 1642, 1598, 1416 cm^{-1}

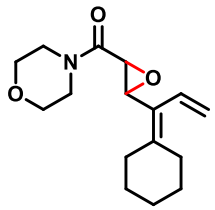
HRMS: (EI) calculated for [$C_{16}H_{23}NO_3$]: 277.1678 $[M]^{+\bullet}$, found 277.1677

3.1.3 Michael-type "nucleophilic" epoxidation [18] Procedure



(3-(1-Cyclohexylideneallyl)oxiran-2-yl)(morpholino)methanone (32)

Notebook: DJL-6-053-B



To a clean and dry RBF, under argon, containing dry THF, ~[0.25 M], was added a [5.50 M] solution of *t*-butyl hydrogen peroxide (TBHP) (1.60 equiv) in decane and the resulting solution was brought to -78 °C with a dry ice/acetone bath. Once at -78 °C, *n*-BuLi (1.10 equiv) was added dropwise, and the mixture was allowed to stir for ~30-45 min. Then the [3]dendralene (1.00 equiv, 0.40 mmol) was added as a solution in THF *ca*. [1.0 M] dropwise and the reaction was allowed to stir for *ca*. 12 h; with warming to rt. Upon TLC analysis, which indicated complete consumption of starting material (see below) the septum was removed from the RBF and solid sodium sulfite was added (to quench any unreacted peroxide), and stirred for ~30 min. The reaction mixture was then diluted with ether and passed through a plug of silica (minimal) / Celite / sand, eluting with ether. After concentration, *via* rotary evaporation, the crude material was purified by column chromatography on silica gel, eluting with 50%

(ether : DCM), to afford the title compound as a viscous clear colorless oil, 61 mg, 55% isolated (74% brsm).

***Note:** For this particular molecule the R_f values of the starting material and product are extremely close. Thus, one must use a less polar eluent system than desired for purification and run the same TLC multiple times (x 3-5) to observe the progression of the reaction. The use of I_2 stain is advised, however, after exposure to this reversible stain it becomes more obvious as the coloration begins to fade from the TLC plate.

TLC: product R_f = 0.35 (40% ether : DCM), UV, I_2, vanillin stain (grey spot)

starting material R_f = 0.32 (40% ether : DCM), UV, I_2, vanillin stain (grey spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.56 (dd, *J* = 17.8, 11.3 Hz, 1H), 5.33 (dd, *J* = 17.5, 1.5 Hz, 1H), 5.10 (dd, *J* = 11.0, 1.5 Hz, 1H), 3.84 (d, *J* = 2.0 Hz, 1H), 3.73 – 3.62 (m, 8H), 3.49 – 3.45 (d, *J* = 2.5 Hz, 1H), 2.42 (t, *J* = 5.3 Hz, 2H), 2.29 (m, 2H), 1.57 (m, 6H)

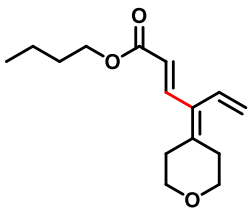
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 146.3, 132.2, 124.0, 115.0, 66.9, 66.9, 56.2, 54.9, 45.7, 42.5, 31.8, 30.8, 28.4, 28.2, 26.7

IR: 2963, 2924, 2858, 1647, 1471, 1438, 1273, 1119 cm^{-1}

HRMS: (EI) calculated for [$C_{16}H_{23}NO_3$]: 277.1678 $[M]^{+\bullet}$, found 277.1676

_n_-Butyl (_E_)-4-(tetrahydro-4_H_-pyran-4-ylidene)hexa-2,5-dienoate (34)

Notebook: DJL-6-009/021



Prepared according to general procedure **B**, 0.94 mmol scale.

Purification: column chromatography on silica gel eluting with 25% then 50% (ether : hexanes), clear colorless oil, 203 mg, 77-86%.

TLC: R_f = 0.20 (20% ether : hexanes), UV, I_2, vanillin stain (blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.68 (ABq, J_{AB} = 15.5 Hz, 1H), 6.32 (dd, J = 17.5, 11.0 Hz, 1H), 5.91 (ABq, J_{AB} = 15.5 Hz, 1H), 5.39 (dd, J = 11.0, 2.0 Hz, 1H), 5.13 (dd, J = 17.8, 1.8 Hz, 1H), 4.15 (t, J = 6.8 Hz, 2H), 3.71 (dt, J = 14.5, 5.5 Hz, 4H), 2.57 (t, J = 5.3 Hz, 2H), 2.53 (t, J = 5.5 Hz, 2H), 1.67 – 1.61 (pent, J = 7.3 Hz, 2H), 1.39 (sex, J = 7.4 Hz, 2H), 0.94 (t, J = 7.5 Hz, 3H)

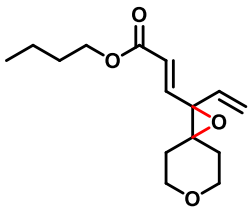
^{13}C NMR: (126 MHz, $CDCl_3$) δ 167.7, 143.0, 140.7, 132.8, 129.6, 120.7, 120.2, 68.8, 68.8, 64.4, 33.2, 31.8, 30.9, 19.3, 13.9

IR: 2957, 2941, 2847, 1713, 1614, 1300 cm^{-1}

HRMS: (EI) calculated for [$C_{15}H_{22}O_3$]: 250.1569 $[M]^{+\bullet}$, found 250.1564

_n_-Butyl (_E_)-3-(2-vinyl-1,6-dioxaspiro[2.5]octan-2-yl)acrylate (35)

Notebook: DJL-6-013/027



Prepared according to general procedure **3.1.1**, 0.78 mmol scale.

Purification: column chromatography on silica gel eluting with 40% then 60% (ether : hexanes), colorless oil, 187 mg, 83-90%.

***Note:** Despite thorough aqueous separatory work-up, benzoic acid still remained in the crude material, which tends to streak through the column during purification. To avoid overlap with

the desired product an initial column volume of 40% (ether : hexanes) helps to remove this by-product off the column. Subsequent elution with 60% (ether : hexanes) provides the desired product free of benzoic acid.

TLC: R_f = 0.35 (40% ether : hexanes), UV, I_2, vanillin stain (blue/ purple spot)

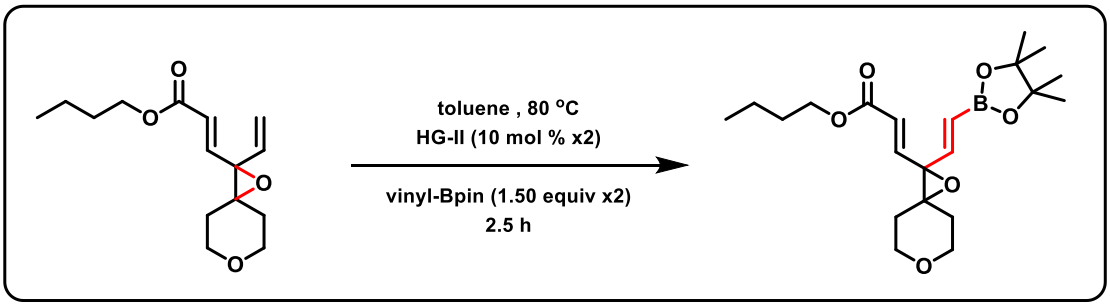
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.04 (ABq, J_{AB} = 15.5 Hz, 1H), 6.02 (ABq, J_{AB} = 15.5 Hz, 1H), 5.99 – 5.91 (dd, J = 17.0, 11.0 Hz, 1H), 5.42 – 5.32 (m, 2H), 4.19 – 4.10 (m, 2H), 3.82 – 3.70 (m, 4H), 1.86 – 1.76 (m, 2H), 1.70 – 1.59 (m, 4H), 1.42 – 1.34 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 166.1, 142.9, 132.1, 124.3, 119.7, 68.6, 67.4, 66.6, 66.5, 64.7, 31.0, 30.9, 30.8, 19.3, 13.8

IR: 2963, 2930, 2847, 1719, 1658, 1377, 1306, 1174 cm^{-1}

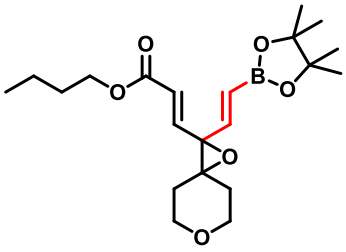
HRMS: (EI) calculated for [$C_{15}H_{23}O_4$]: 267.1596 $[M+H]^+$, found 267.1597

3.2 Cross-metathesis [19] Procedure



***n*-Butyl (*E*)-3-(2-((*E*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1,6-dioxaspiro[2.5]octan-2-yl)acrylate (36)**

Notebook: DJL-6-052



To a clean and dry two-necked RBF containing the starting vinylic epoxide (1.00 equiv, 0.21 mmol) in dry toluene (*ca*. [0.20 M]) was added vinyl-Bpin (1.50 equiv) followed by a solution of HG-II catalyst (10 mol %) in dry toluene, *ca*. [0.20 M]. The following solution was then brought to 80 °C, with stirring, for 45–60 min. at which point a second addition of both, 'neat,' vinyl-Bpin (1.50 equiv) and HG-II (10 mol %) in dry toluene were added at 80 °C. The resulting mixture was allowed to stir for a total of 2.5 h, at which point TLC analysis (see below) indicated near complete consumption of starting material and the reaction was allowed to cool to rt. It was then diluted with ether and passed through a plug of silica gel (minimal) / Celite / sand, eluting with ether. After concentration, *via* rotary evaporation, the crude material

was purified by column chromatography on silica gel, eluting with 50% (ether : hexanes), to afford the title compound as a viscous light yellow oil, 54.5 mg, 66%.

TLC: product R_f = 0.40 (60% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.06 (ABq, J_{AB} = 16.0 Hz, 1H), 6.66 (ABq, J_{AB} = 18.5 Hz, 1H), 6.02 (ABq, J_{AB} = 16.0 Hz, 1H), 5.75 (ABq, J_{AB} = 18.5 Hz, 1H), 4.16 – 4.12 (m, 2H), 3.78 – 3.74 (m, 4H), 1.79 (m, 2H), 1.64 (m, 4H), 1.39 (m, 2H), 1.27 (d, J = 1.5 Hz, 12H), 0.94 (t, J = 7.3 Hz, 3H)

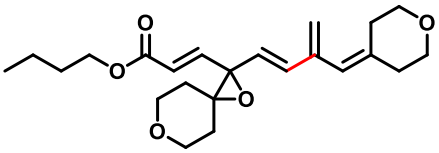
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 145.1, 142.3, 124.3, 124.3, 83.7, 69.2, 68.4, 66.6, 66.5, 64.7, 31.0, 30.8, 24.9, 24.9, 19.3, 13.8

IR: 2968, 2930, 2852, 1719, 1636, 1455, 1355, 1146 cm^{-1}

HRMS: (EI) calculated for [$C_{21}H_{33}{}^{10}BO_6$]: 391.2407 $[M]^{+\bullet}$, found 391.2406

***n*-Butyl (*E*)-3-(2-((*E*)-3-((tetrahydro-4*H*-pyran-4-ylidene)methyl)buta-1,3-dien-1-yl)-1,6-dioxaspiro[2.5]octan-2-yl)acrylate (37)**

Notebook: DJL-6-078



Prepared according to general procedure **A**, 0.157 mmol scale.

Purification: column chromatography on silica gel eluting with 40% (ether : hexanes), clear colorless oil, 28.3 mg, 46%.

TLC: R_f = 0.44 (60% ether : hexanes), UV, I_2, vanillin (brown spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.05 (ABq, J_{AB} = 15.5 Hz, 1H), 6.34 (d, J = 16.0 Hz, 1H), 6.02 (ABq, J_{AB} = 15.5 Hz, 1H), 5.75 (m, 2H), 5.23 (d, J = 1.5 Hz, 1H), 5.00 (s, 1H), 4.18 – 4.11 (m, 2H), 3.82 – 3.70 (m, 6H), 3.62 (t, J = 5.5 Hz, 2H), 2.38 – 2.26 (bm, 4H), 1.81 (m, 2H), 1.67 – 1.59 (m, 4H), 1.44 – 1.36 (m, 3H), 1.33 – 1.25 (m, 1H), 0.97 – 0.91 (t, J = 7.5 Hz, 3H)

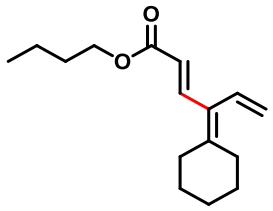
^{13}C NMR: (126 MHz, $CDCl_3$) δ 166.1, 143.0, 141.3, 139.8, 136.5, 124.6, 124.1, 120.4, 119.4, 69.7, 69.1, 69.1, 67.3, 66.5, 64.8, 37.1, 31.2, 31.0, 31.0, 30.8, 30.5, 19.3, 13.8

IR: 2957, 2935, 2852, 1719, 1658, 1471, 1377, 1295 cm^{-1}

HRMS: (EI) calculated for [$C_{23}H_{32}O_5$]: 388.2250 [M]$^{+\bullet}$, found 388.2249

***n*-Butyl (*E*)-4-cyclohexylidenehexa-2,5-dienoate (38)**

Notebook: MRM-1-075



Prepared according to general procedure **B**, 2.00 mmol scale.

Purification: column chromatography on silica gel eluting with 1 CV pentanes then 2% then 5% (ether : hexanes), colorless oil, 454 mg, 92%.

TLC: R_f = 0.43 (10% ether : hexanes), UV, I_2, vanillin (purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.77 (q_{AB}, J_{AB} = 16.0 Hz, 1H), 6.33 (dd, J = 17.7, 11.1 Hz, 1H), 5.87 (q_{AB}, J_{AB} = 16.0 Hz, 1H), 5.36 – 5.31 (m, 1H), 5.10 (m, 1H), 4.14 (t, J = 6.7 Hz, 2H), 2.48 – 2.40 (m, 2H), 2.40 – 2.33 (m, 2H), 1.63 (m, 8H), 1.44 – 1.36 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H)

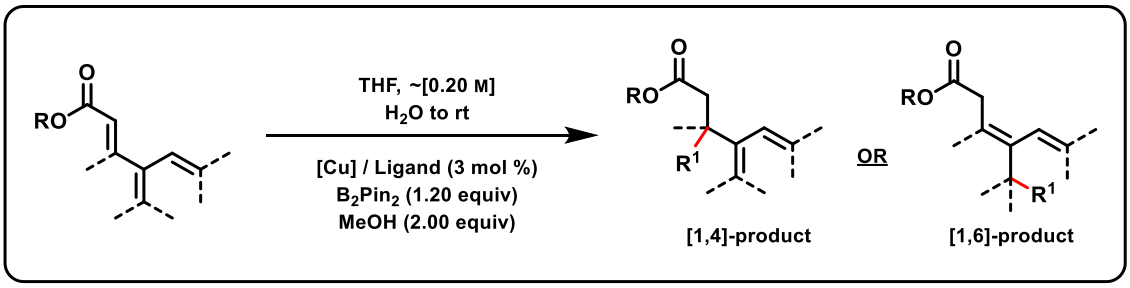
^{13}C NMR: (125 MHz, $CDCl_3$) δ 168.0, 149.8, 141.7, 133.6, 128.0, 119.6, 119.3, 64.2, 32.9, 31.4, 31.0, 28.6, 28.6, 26.8, 19.3, 13.9

IR: 2962 (w), 2934 (m), 2856 (w), 1710 (s), 1610 (m), 1455 (w), 1383 (w) cm^{-1}

HRMS: (EI) calculated for [$C_{16}H_{24}O_2$] : 248.1776 $[M]^{+\bullet}$, found 248.1769

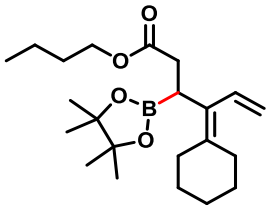
3.3 Regioselective conjugate additions

3.3.1 Copper-catalyzed conjugate borylation: General procedure



_n_-Butyl 4-Cyclohexylidene-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-enoate (39)

Notebook: MRM-1-078



To a clean and dry RBF was added CuCl (3 mol %), triphenylphosphine (4 mol %) and NaO-*t*-Bu (10 mol %) in a glove box. The sealed RBF was then removed from the glove box and dry THF, ~[0.50 M], was added slowly, washing the walls of the flask to bring all of the salts into solution; this solution was then stirred at rt for *ca*. 20–30 min. The flask was then immersed in a rt water bath, followed by the addition of B_2Pin_2 (1.20 equiv) in one portion, subsequent washing of the RBF's walls with minimal THF and continued stirring for *ca*. 15–20 min. Then a solution of the [3]dendralene (1.00 equiv, 0.50 mmol) in THF, *ca*. [1.0 M], was added dropwise, followed by dropwise addition of MeOH (2.00 equiv). The resulting reaction mixture was allowed to stir overnight, *ca*. 12-16 h, at which time the reaction's progress was checked *via* TLC analysis (see below). Once complete, the reaction was diluted with ether and

stirred for 5-10 min, followed by direct transfer to an appropriately sized plug of silica gel / Celite / sand / Celite / sand, eluting with ether. After concentration under vacuum the resulting crude oil was then subjected to column chromatography on silica gel eluting with 15% (ether : hexanes), to afford the title compound as a clear colorless oil, 173 mg, 92%.

***Note:** These particular boronates are exceedingly robust, relative to sp and sp^2 analogues.

TLC: R_f = 0.25 (10% ether : hexanes), UV, I_2, vanillin (blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.67 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.16 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.01 (dd, *J* = 11.5, 1.0 Hz, 1H), 4.09 – 3.96 (m, 2H), 2.83 – 2.77 (t, *J* = 7.8 Hz, 1H), 2.71 (dd, *J* = 15.7, 8.6 Hz, 1H), 2.38 – 2.25 (m, 3H), 2.25 – 2.14 (m, 2H), 1.71 – 1.44 (m, 8H), 1.41 – 1.32 (m, 2H), 1.22 (s, 6H), 1.19 (s, 6H), (t, *J* = 7.4 Hz, 3H)

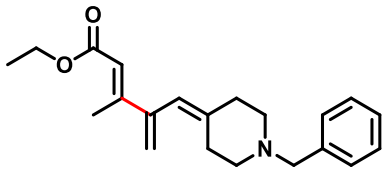
^{13}C NMR: (125 MHz, $CDCl_3$) δ 174.1, 140.6, 135.1, 128.8, 113.1, 83.5, 64.2, 35.8, 32.6, 31.2, 30.9, 28.6, 28.5, 27.1, 24.9, 24.8, 19.3, 13.9

IR: 2973 (w), 2928 (m), 2856 (w), 1738 (s), 1455 (w), 1361 (m), 1317 (s) cm^{-1}

HRMS: (EI) calculated for [$C_{22}H_{37}{}^{10}BO_4$]: 375.2821 $[M]^{+\bullet}$, found 375.2822

Ethyl (*E*)-4-((1-benzylpiperidin-4-ylidene)methyl)-3-methylpenta-2,4-dienoate (40)

Notebook: DJL-5-187



Prepared according to general procedure **A**, 1.75 mmol scale.

Purification: column chromatography on silica gel eluting with 20% then 40% (ether : hexanes), light yellow oil, 515 mg, 90%.

TLC: R_f = 0.33 (40% ether : hexanes), UV, I_2, vanillin stain (pale orange spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 4H), 7.25 (m, 1H), 5.93 (s, 1H), 5.75 (s, 1H), 5.55 (d, *J* = 0.5 Hz, 1H), 5.14 (s, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.52 (s, 2H), 2.54 – 2.47 (t, *J* = 5.8 Hz, 2H), 2.40 (t, *J* = 5.5 Hz, 2H), 2.34 – 2.28 (m, 7H), 1.30 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 167.4, 154.1, 146.0, 141.4, 138.7, 129.2, 128.3, 127.1, 121.5, 118.8, 118.0, 63.1, 59.9, 55.3, 54.8, 36.2, 29.6, 15.5, 14.5

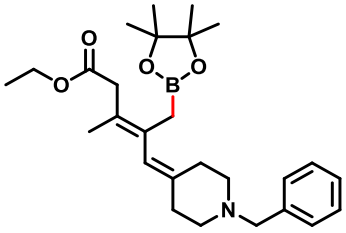
IR: 3084, 3034, 2935, 2897, 2797, 2795, 1713, 1620, 1185 cm^{-1}

HRMS: (EI) calculated for [$C_{21}H_{27}NO_2$]: 325.2042 $[M]^{+\bullet}$, found 325.2044

(E:Z): > 20:1 , see spectra section

Ethyl (*E*)-5-(1-benzylpiperidin-4-ylidene)-3-methyl-4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pent-3-enoate (41)

Notebook: DJL-5-191



Prepared according to general procedure **3.3.1**, 0.50 mmol scale.

Purification: column chromatography on silica gel eluting with 20% then 40% (ether : DCM), viscous light bronze oil, 179 mg, 79%.

TLC: R_f = 0.27 (40% ether : DCM), UV, I_2, vanillin stain (lavender on front of plate/fuchsia on back of plate)

^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.30 (m, 4H), 7.24 (m 1H), 5.59 (s, 1H), 4.09 (q, *J* = 7.0 Hz, 2H), 3.51 – 3.48 (s, 2H), 3.07 (s, 2H), 2.46 – 2.42 (t, *J* = 5.4 Hz, 2H), 2.41 – 2.34 (t, *J* = 5.4

HZ, 2H), 2.26 – 2.21 (t, *J* = 5.4 Hz, 2H), 2.15 (t, *J* = 5.4 Hz, 2H), 1.70 (m, 5H), 1.24 – 1.19 (m, 15H)

^{13}C NMR: (151 MHz, cdcl$_3$) δ 172.6, 138.8, 137.4, 131.0, 129.3, 128.3, 127.0, 124.8, 122.8, 83.2, 63.2, 60.3, 55.2, 54.4, 41.0, 35.5, 29.6, 24.9, 24.9, 18.3, 14.4

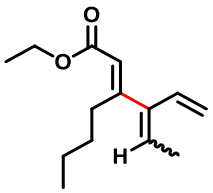
IR: 2985, 2930, 2797, 1730, 1455, 1322 cm^{-1}

HRMS: (EI) calculated for [$C_{27}H_{40}{}^{10}BNO_4$]: 452.3087 $[M]^{+\bullet}$, found 452.3086

(*E:Z*): Assigned in accordance with the [1,6]-borylation shown below.

Ethyl (2*E*)-3-(penta-1,3-dien-3-yl)hept-2-enoate (42)

Notebook: DJL-6-088



Prepared according to general procedure **A**, 1.00 mmol scale.

Purification: column chromatography on silica gel eluting with 1 CV hexanes then 2% (ether : hexanes), clear colorless oil, 151 mg, 68%.

TLC: R_f = 0.41 (3% ether : hexanes), UV, I_2, vanillin stain (light blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 17.5, 11.5 Hz, 0.5H), 6.40 – 6.16 (dd, *J* = 17.3, 10.8 Hz, 0.5H), 5.76 (s, 0.5H), 5.65 – 5.52 (m, 1.5H), 5.24 (d, *J* = 11.0 Hz, 0.5H), 5.09 (dd, *J* = 14.4, 13.7 Hz, 0.5H), 4.95 (m, 1H), 4.17 (dq, *J* = 14.2, 7.1 Hz, 4H), 2.78 – 2.69 (m, 2H), 1.79 (d, *J* = 7.1 Hz, 1.4H), 1.69 (d, *J* = 7.1 Hz, 1.6H), 1.38 – 1.25 (m, 7H), 0.92 – 0.85 (m, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 166.8, 166.3, 162.7, 159.3, 143.3, 141.6, 138.5, 131.6, 127.2, 126.4, 119.8, 118.0, 117.8, 113.7, 59.9, 59.7, 32.4, 31.2, 30.9, 30.5, 23.4, 23.1, 15.1, 14.5, 14.4, 14.1, 14.0, 14.0

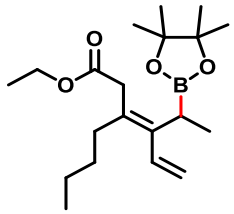
IR: 2957, 2930, 2863, 1719, 1636, 1163 cm^{-1}

HRMS: (EI) calculated for [$C_{14}H_{23}O_2$]: 223.1698 $[M+H]^+$, found 223.1700

(E:Z): α:β > 20:1 , γ:δ ~1.2:1 (see spectra section)

Ethyl (*E*)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-3-ylidene)heptanoate (43)

Notebook: DJL-5-254



Prepared according to general procedure **3.3.1**, 0.18 mmol scale.

Purification: column chromatography on silica gel eluting with 10% then 15% (ether : hexanes), colorless oil, 45.5 mg, 72%.

TLC: R_f = 0.15 (7% ether : hexanes), UV, I_2, vanillin stain (blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.59 (dd, *J* = 17.8, 11.3 Hz, 1H), 5.18 – 5.12 (m, 1H), 5.07 – 5.03 (m, 1H), 4.13 – 4.08 (m, 2H), 3.21 – 3.07 (ABq, J_{AB} = 15.0 Hz, 2H), 2.35 – 2.28 (m, 2H), 2.21 – 2.15 (m, 1H), 1.40 – 1.33 (m, 2H), 1.32 – 1.27 (m, 2H), 1.25 – 1.22 (t, *J* = 7.3 Hz, 3H), 1.20 (d, *J* = 10.0 Hz, 12H), 1.12 (d, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 172.0, 138.5, 134.6, 131.5, 114.0, 83.2, 60.6, 39.5, 33.4, 31.1, 25.0, 24.8, 22.8, 15.3, 14.3, 14.2

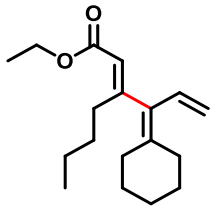
IR: 2985, 2926, 2863, 1735, 1625, 1460 cm^{-1}

HRMS: (EI) calculated for [$C_{20}H_{35}{}^{10}BO_4$]: 349.2665 $[M]^{+\bullet}$, found 349.2655

(E:Z): > 20 : 1 , determined *via* NOESY 2D analysis (see spectra section)

Ethyl (*E*)-3-(1-cyclohexylideneallyl)hept-2-enoate

Notebook: DJL-5-238



Prepared according to general procedure **A**, 1.57 mmol scale.

Purification: column chromatography on silica gel eluting with 1 CV hexanes then 2% (ether : hexanes), colorless oil, 330 mg, 76%.

TLC: R_f = 0.32 (2% ether : hexanes), UV, I_2, vanillin stain (purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.73 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.56 (s, 1H), 5.06 – 4.92 (m, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.76 – 2.61 (m, 2H), 2.33 (m, 2H), 2.20 – 2.12 (t, *J* = 5.8 Hz, 2H), 1.60 – 1.50 (m, 6H), 1.39 – 1.32 (m, 4H), 1.29 (t, *J* = 7.3 Hz, 3H), 0.88 (m, 3H)

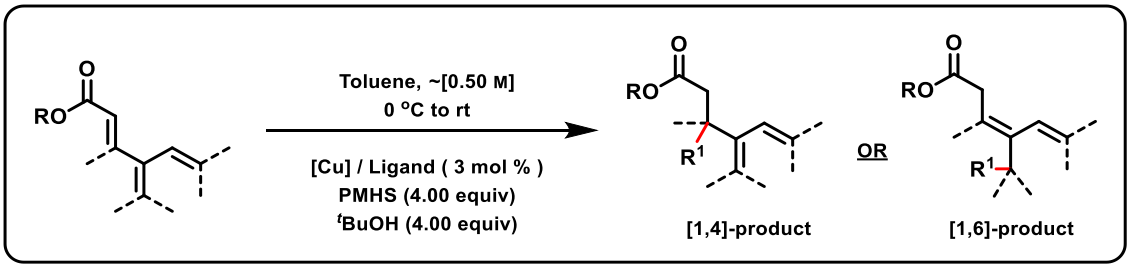
^{13}C NMR: (126 MHz, $CDCl_3$) δ 166.5, 161.7, 140.1, 133.6, 132.6, 119.6, 115.2, 59.8, 33.4, 33.1, 30.6, 30.1, 28.6, 28.3, 26.9, 23.5, 14.5, 14.1

IR: 2962, 2934, 2856, 1716, 1638, 1444 cm^{-1}

HRMS: (EI) calculated for [$C_{18}H_{28}O_2$]: 276.2089 $[M]^{+\bullet}$, found 276.2083

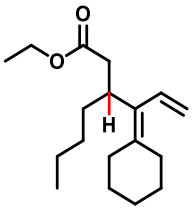
(E:Z): > 20:1 (see spectra section)

3.3.2 Copper-catalyzed hydride addition procedure



Ethyl 3-(1-cyclohexylideneallyl)heptanoate

Notebook: DJL-5-255



To a clean and dry BRF was added CuCl (3 mol %), (*R*)-DTBM-SegPhos (4 mol %) and NaO-*t*-Bu (10 mol %) in a glove box. The sealed RBF was then removed from the glove box and dry toluene, ~[0.50 M], was added slowly, washing the walls of the flask to bring all of the salts into solution; this solution was then stirred at rt for 20–30 min. Then the flask was immersed in a rt water bath, followed by the dropwise addition of PMHS (2.00 equiv), the RBF's walls were then washed with minimal toluene and the reaction was stirred for 15–20 min. Then the rt water bath was exchanged for a 0 °C, NaCl/ice/water, bath. Once cooled to 0 °C, a solution of the [3]dendralene (1.00 equiv, 0.30 mmol) in toluene, ~[1.0 M], was added dropwise, followed by dropwise addition of *t*-butanol (2.00 equiv), more PMHS (2.00 equiv) and the remainder of *tert*-butanol (2.00 equiv). The resulting reaction mixture was allowed to stir overnight, *ca*. 12-16 h, and the reaction progress was checked *via* TLC analysis which indicated slight product formation but an incomplete reaction (see **Note** and TLC conditions

below). The reaction was eventually quenched by addition of saturated aqueous $NaHCO_3$ and stirred at rt for 1–2 h. This mixture was then transferred to a separatory funnel where it was extracted with ether (x 3), dried over anhydrous Na_2SO_4, filtered from salts and concentrated by rotary evaporation. Purification by column chromatography on silica gel, eluting with pentanes, then 1%, and then 2% (ether : hexanes), afforded the title compound as a clear colorless oil, 8 mg, 9% isolated.

***Note:** The analogous reaction with B_2Pin_2 provided no product at all, and only starting material was observed after many trials and variations of reaction conditions. For the reaction above, after ~12 h more PMHS was added (1.00 equiv) and checked after 6 more h. Then more PMHS was added (2.00 equiv) along with methanol (2.00 equiv), and the reaction was allowed to stir for another 16 h and then quenched as stated above.

TLC: R_f = 0.52 (7 % ether : hexanes), UV, I_2, vanillin stain (blue spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.15 (dd, *J* = 17.5, 11.5 Hz, 1H), 5.23 – 5.19 (m, 1H), 5.01 – 4.97 (m, 1H), 4.13 – 4.03 (m, 2H), 3.22 – 3.11 (m, 1H), 2.33 (m, 4H), 2.25 – 2.19 (m, 2H), 1.60 – 1.46 (m, 8H), 1.26 (m, 4H), 1.22 (t, *J* = 7.0 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 173.2, 125.7, 124.9, 108.8, 96.8, 60.2, 39.9, 36.5, 33.3, 32.5, 31.7, 31.7, 30.9, 30.5, 29.8, 29.0, 28.7, 27.2

IR: 2963, 2930, 2863, 2176, 1741, 1273, 1113, 1047 cm^{-1}

HRMS: (EI) calculated for $[C_{18}H_{30}O_2]$: 278.2246 $[M]^{+\bullet}$, found 278.2257

2.7. Experimental References

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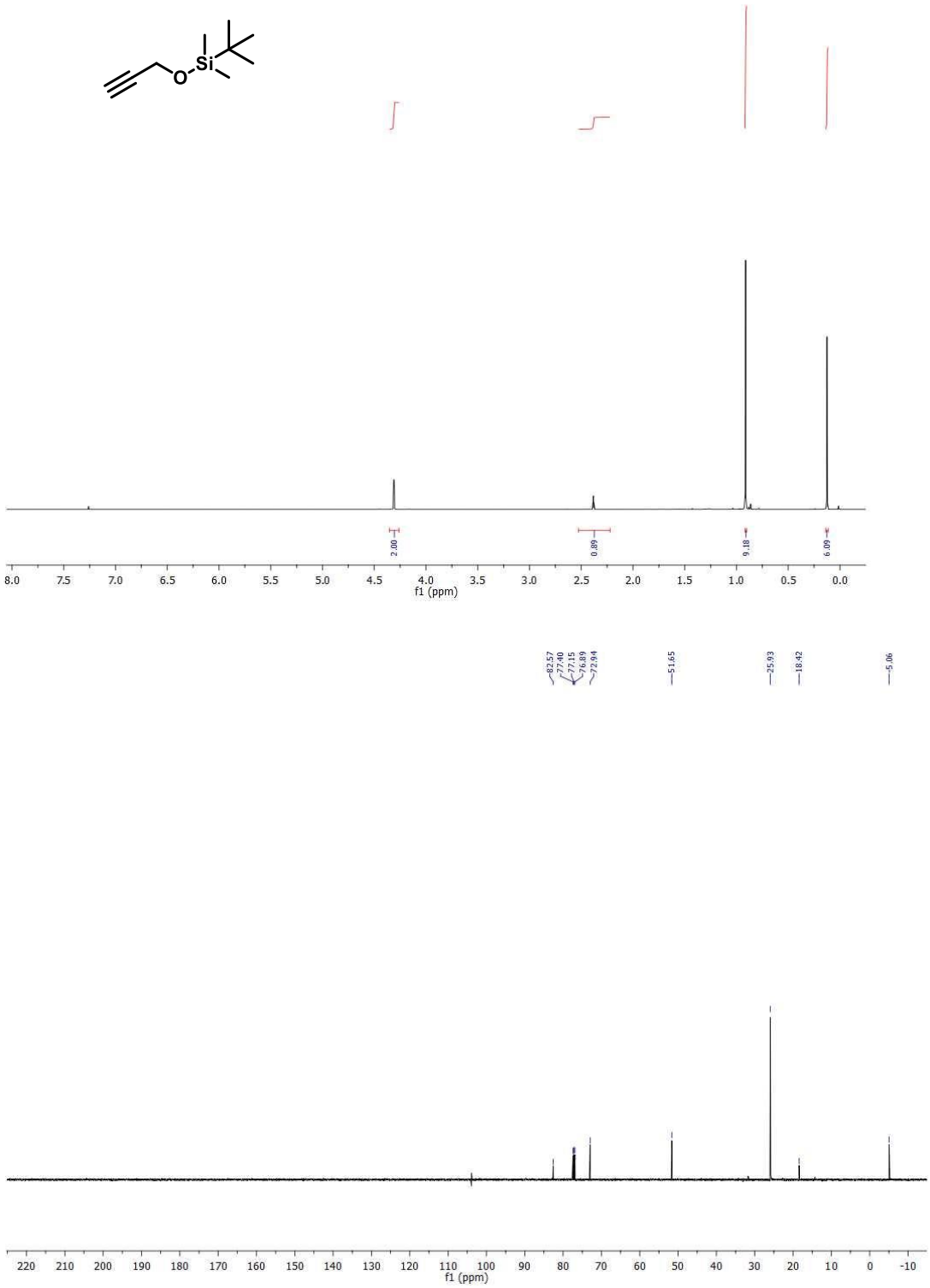
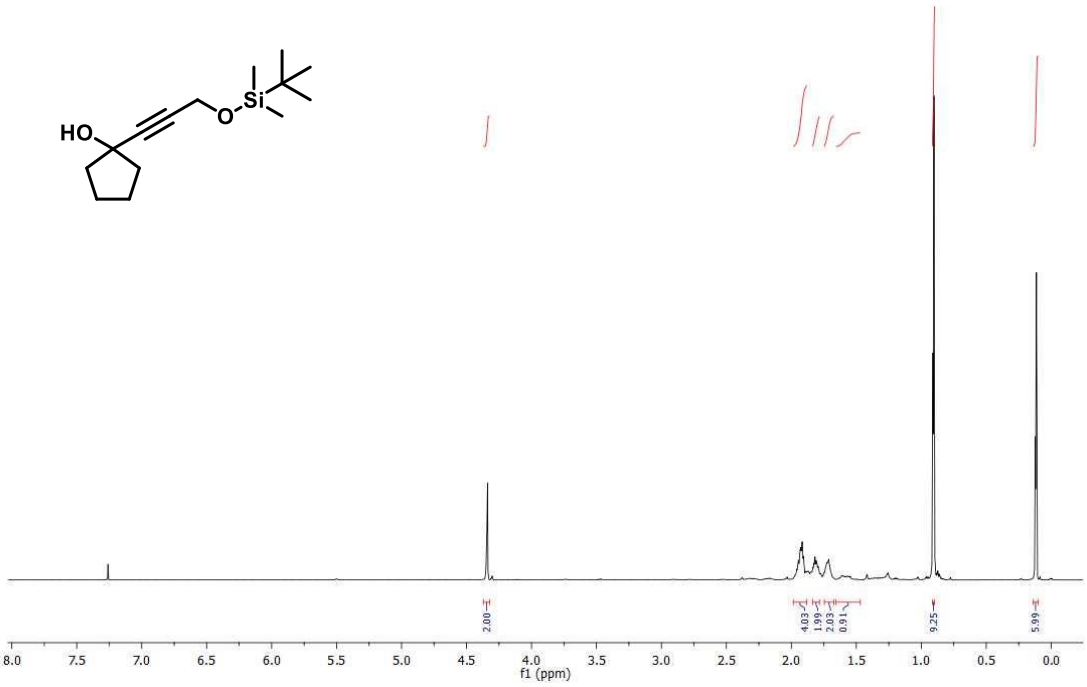
2.8. Spectral Data

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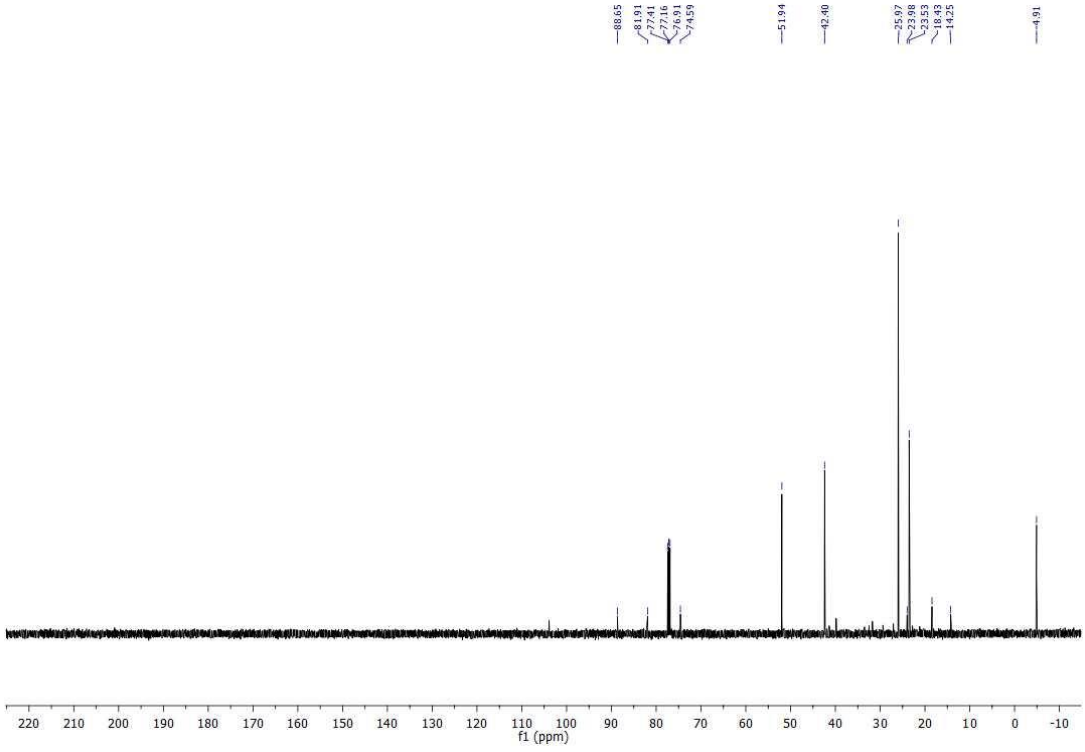
2.07
0.91
9.25
5.99
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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77.16
76.91
74.59
51.94
42.40
35.97
23.98
23.53
18.48
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-4.91
220
210
200
190
180
170
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120
110
100
90
80
70
60
50
40
30
20
10
0
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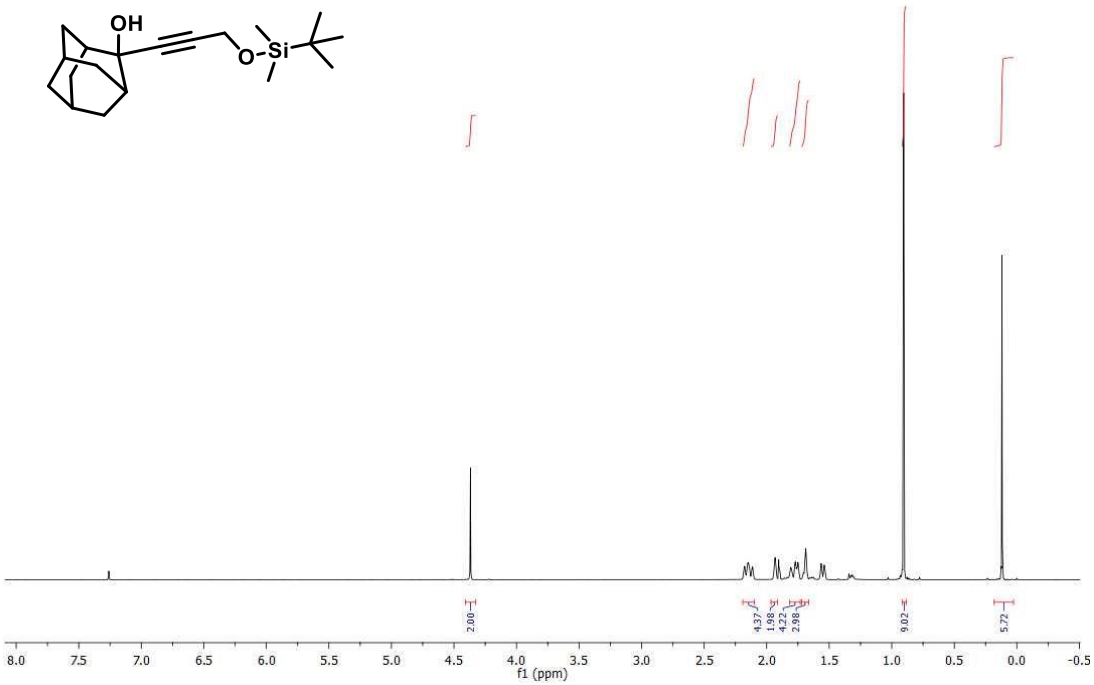
f1 (ppm)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4.22
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8.0
7.5
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6.0
5.5
5.0
4.5
4.0
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3.0
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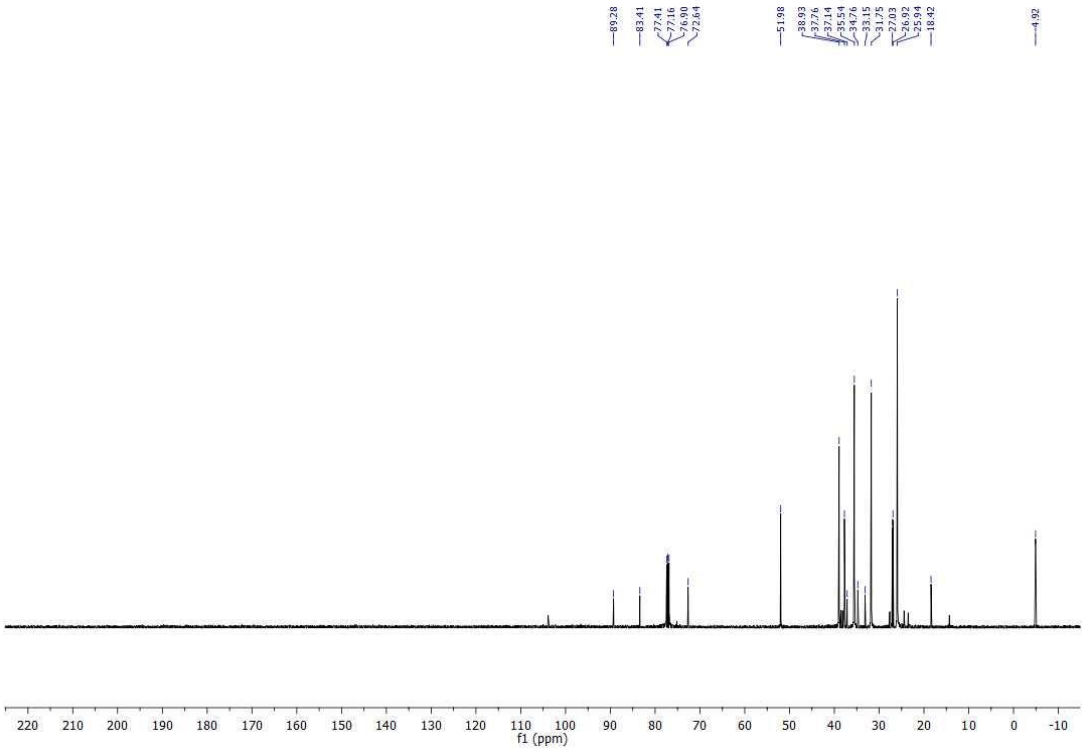
f1 (ppm)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77.41
77.16
76.90
72.64
51.98
38.93
37.76
37.14
35.54
34.76
33.15
31.75
27.03
26.92
25.94
18.42
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220
210
200
190
180
170
160
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40
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0
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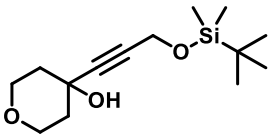
f1 (ppm)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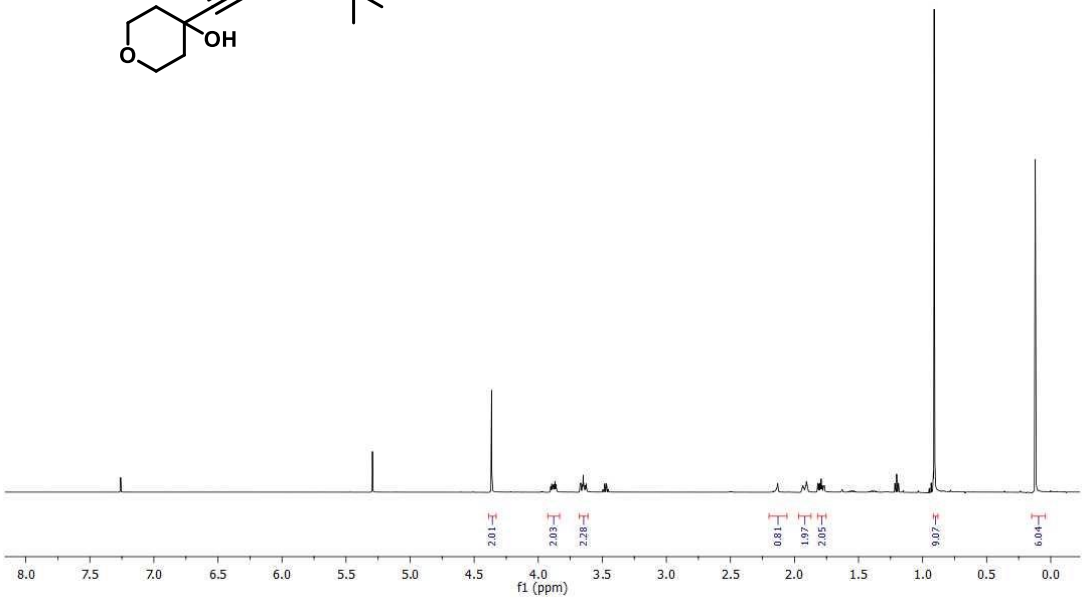
OH
O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0.81
1.97
2.05
9.07
6.04
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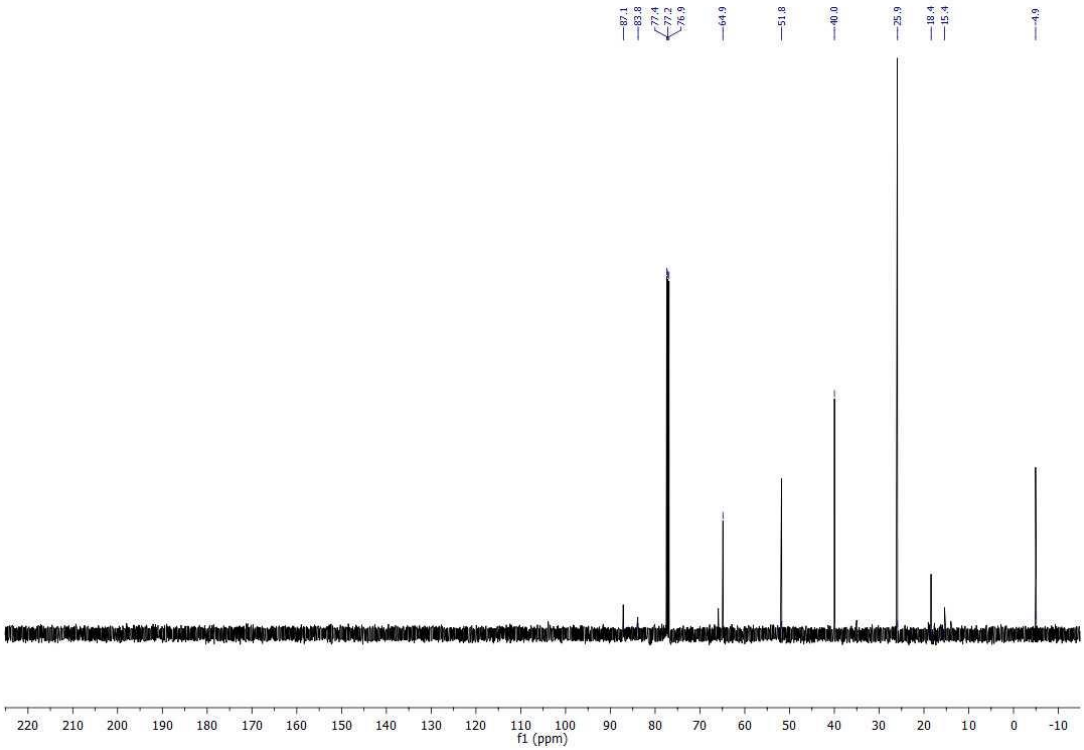
f1 (ppm)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76.9
64.9
51.8
40.0
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18.4
15.4
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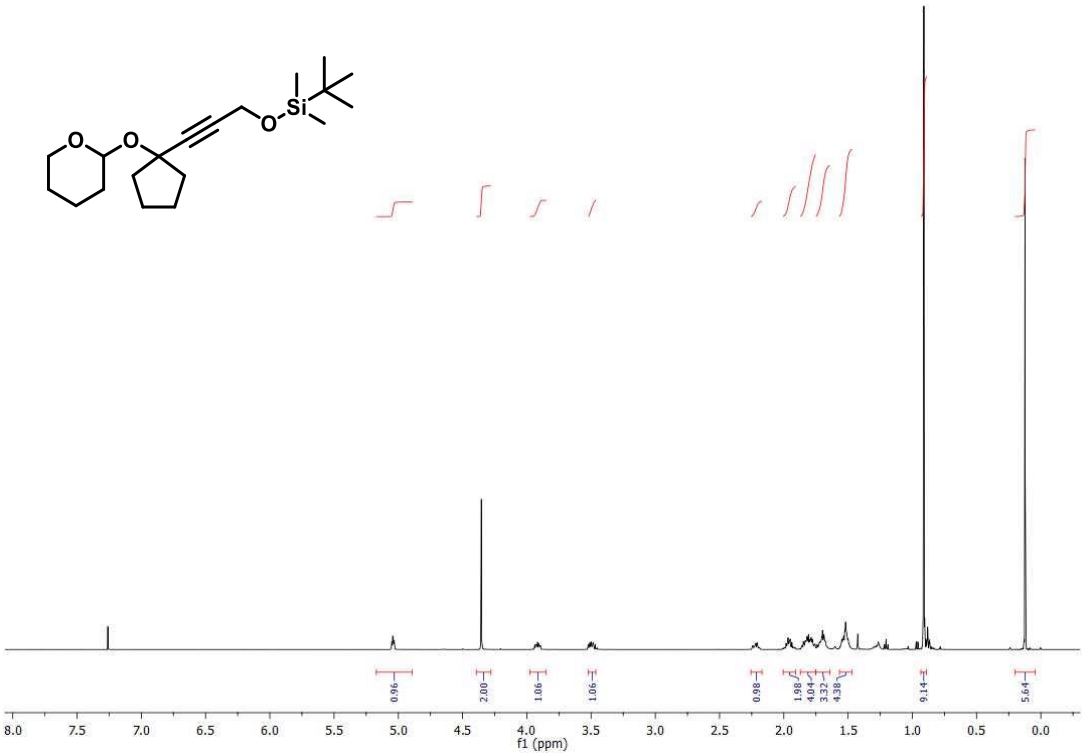
f1 (ppm)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O
O
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1.06
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1.98
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5.64
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
3.0
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1.0
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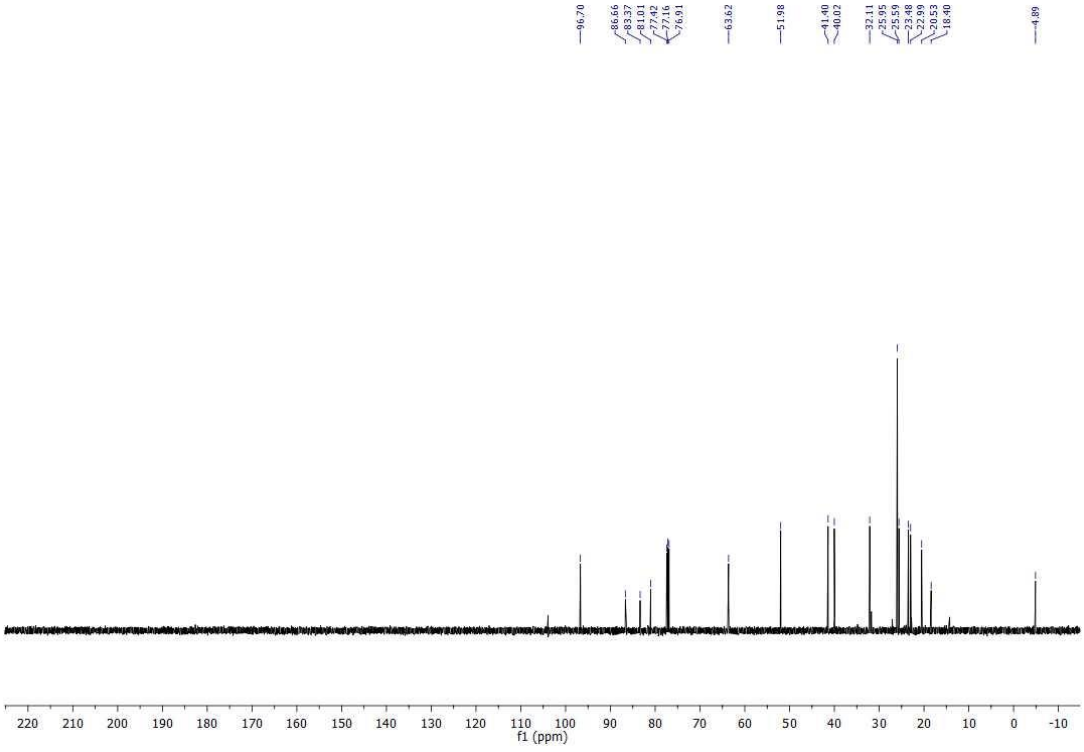
0.0
f1 (ppm)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76.91
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40.02
32.11
25.95
25.59
23.48
22.99
20.53
18.40
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220
210
200
190
180
170
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100
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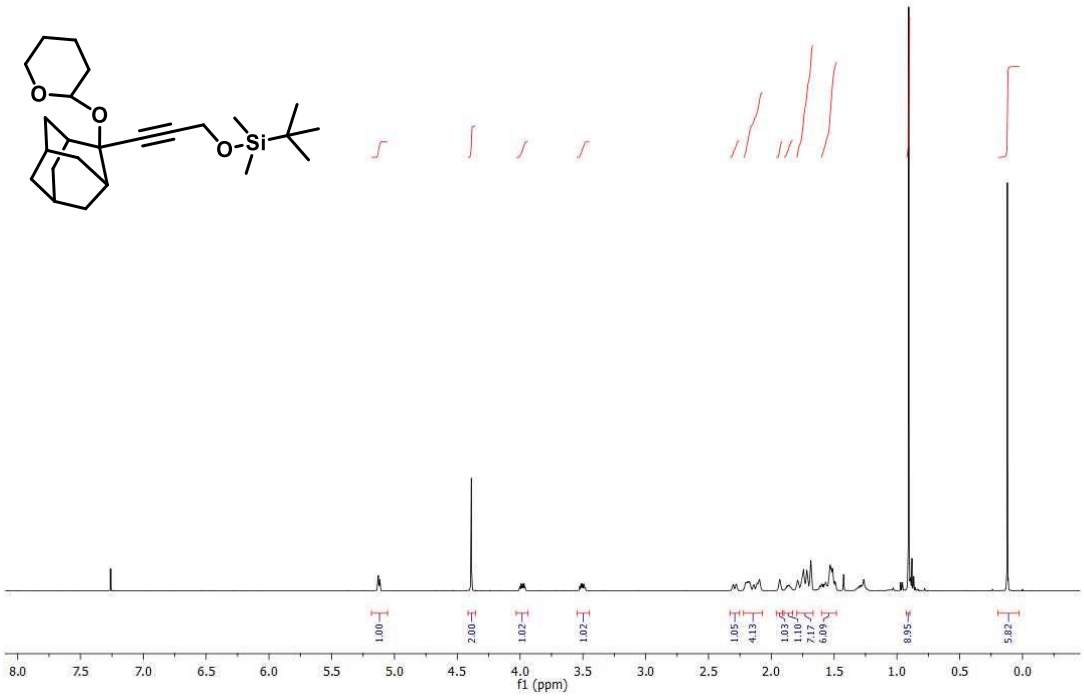
30
20
10
0
-10
f1 (ppm)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1.02
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1.10
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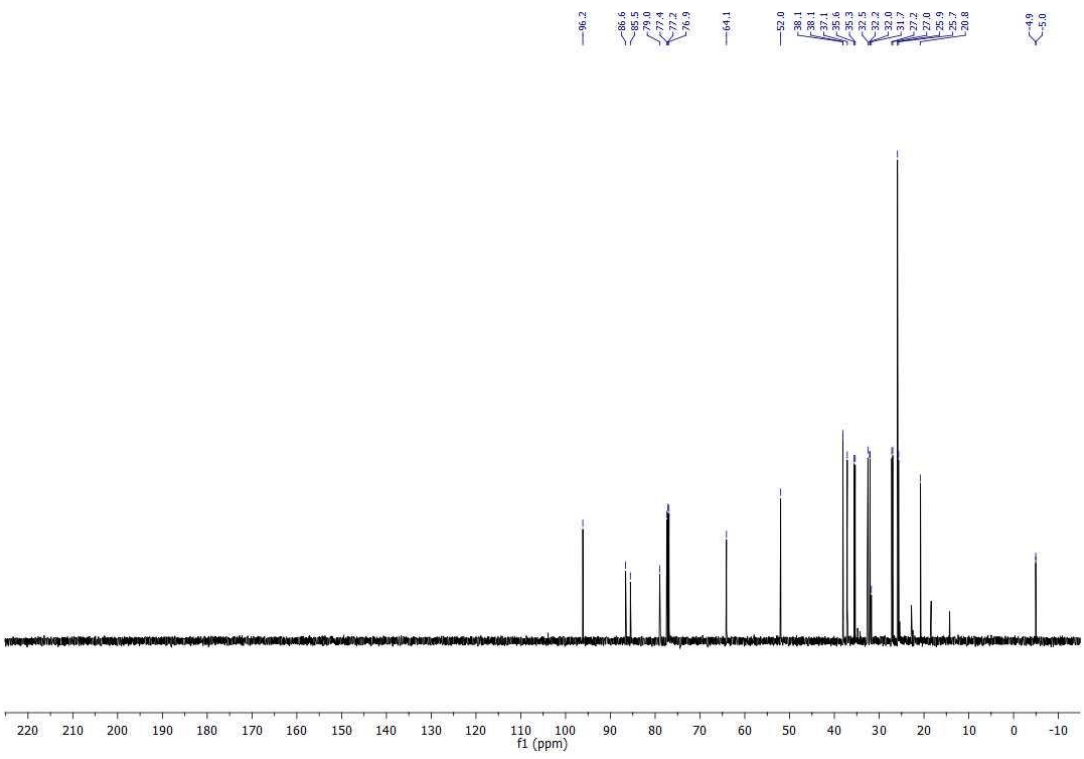
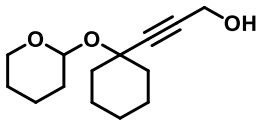
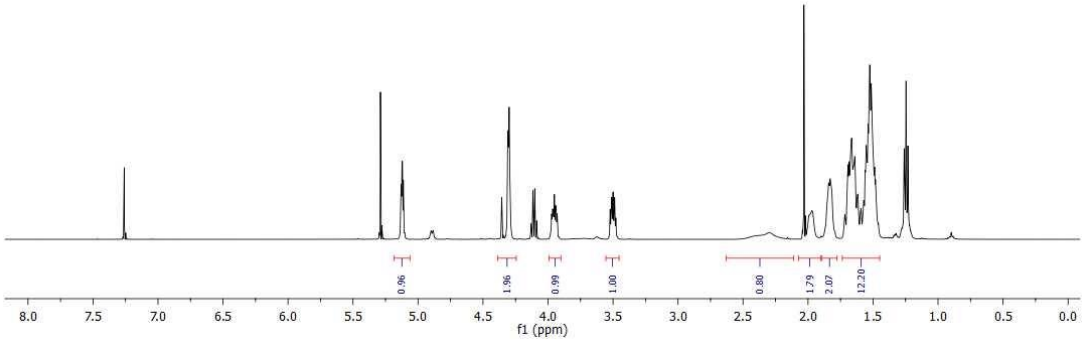
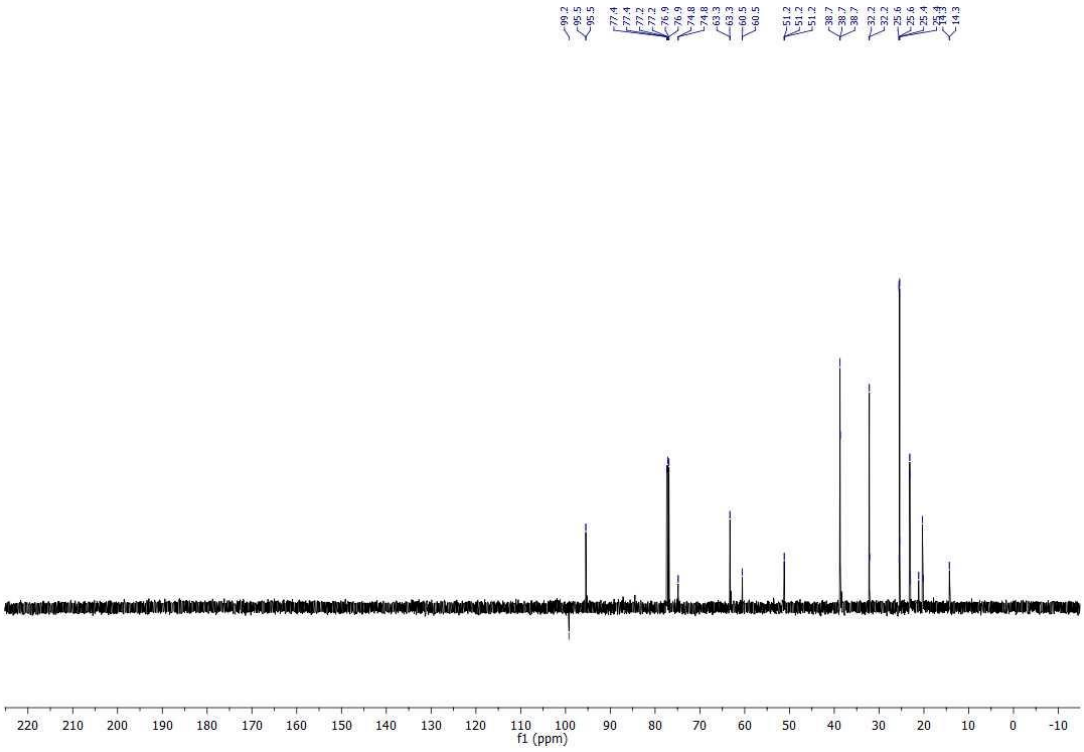
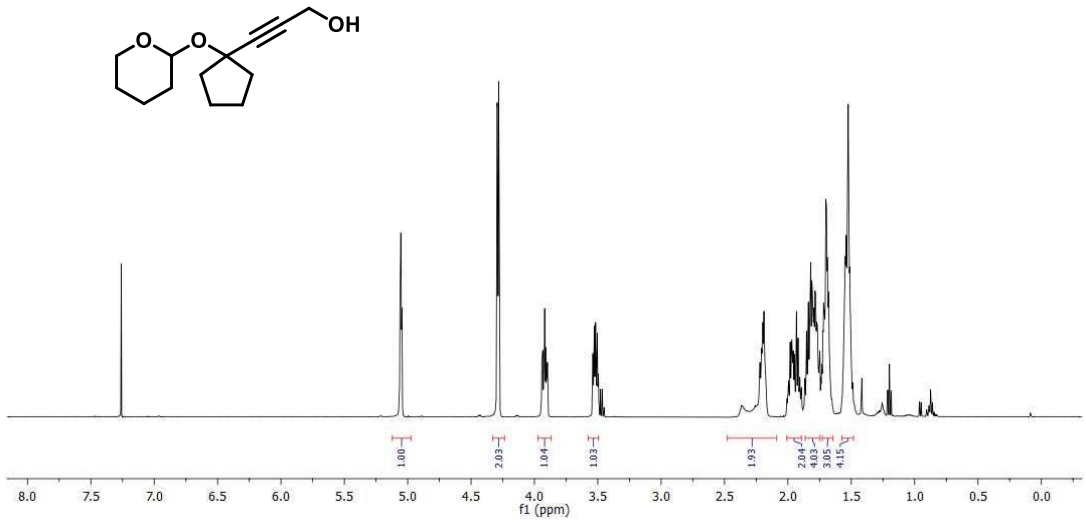
5.82
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

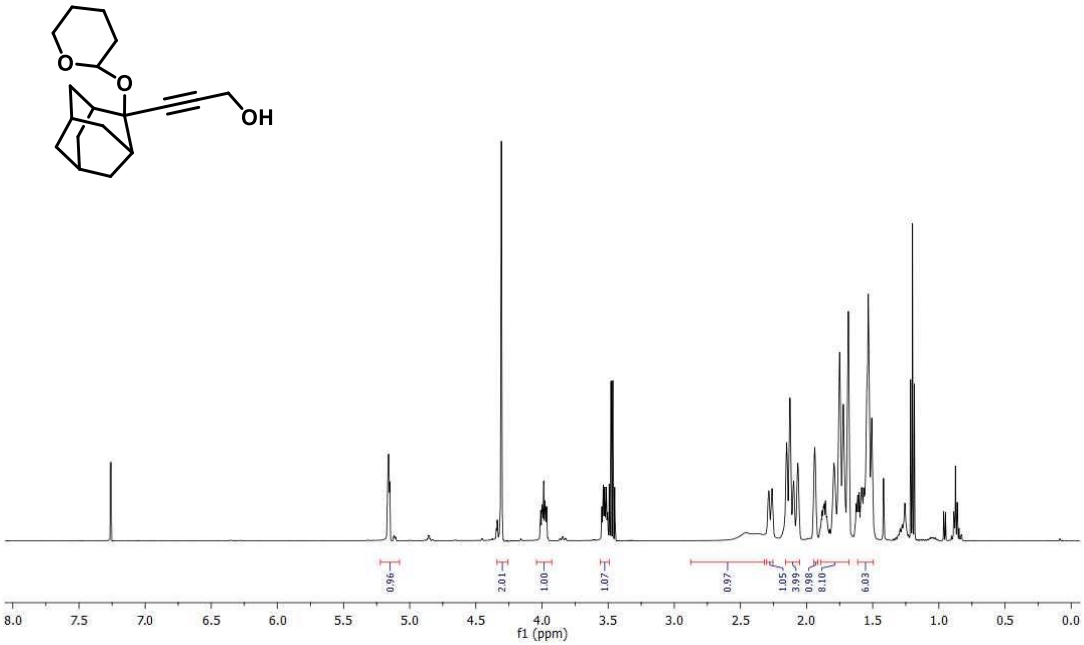

96.2
86.6
85.5
79.0
77.4
77.2
76.9
64.1
52.0
38.1
38.1
37.1
35.6
35.3
32.5
32.2
32.0
31.7
27.2
27.0
25.9
25.7
20.8
-4.9
-5.0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

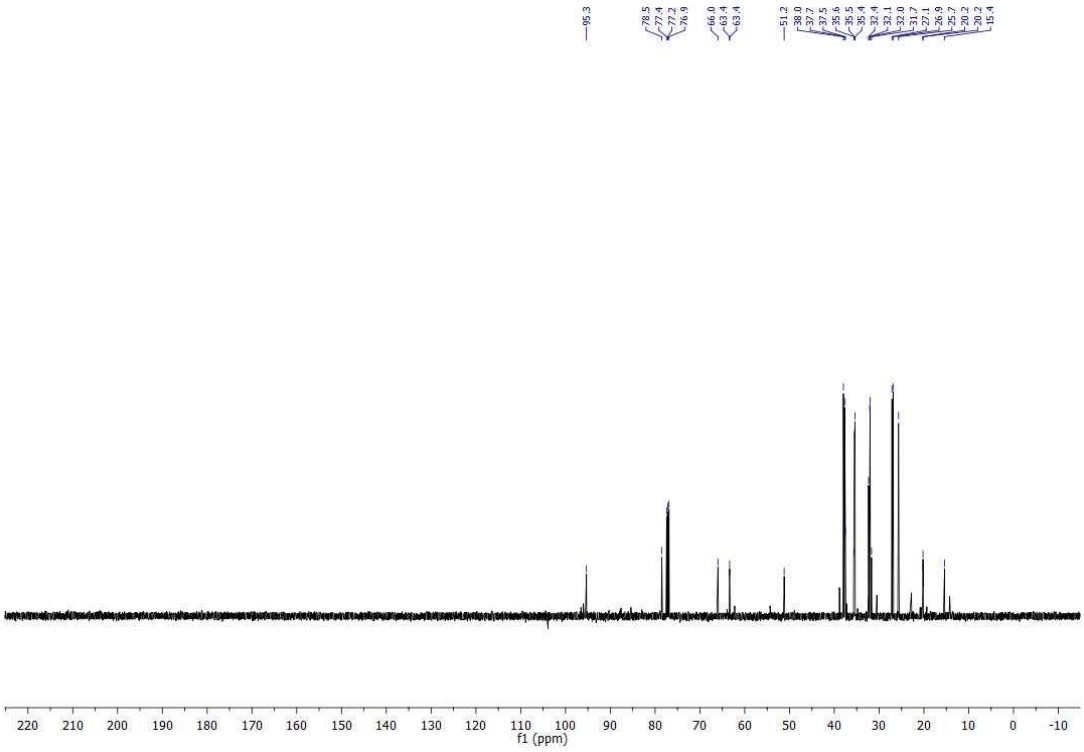

O
O
OH

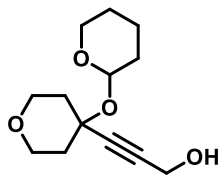

0.96
1.96
0.99
1.00
0.80
1.79
2.07
12.20
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

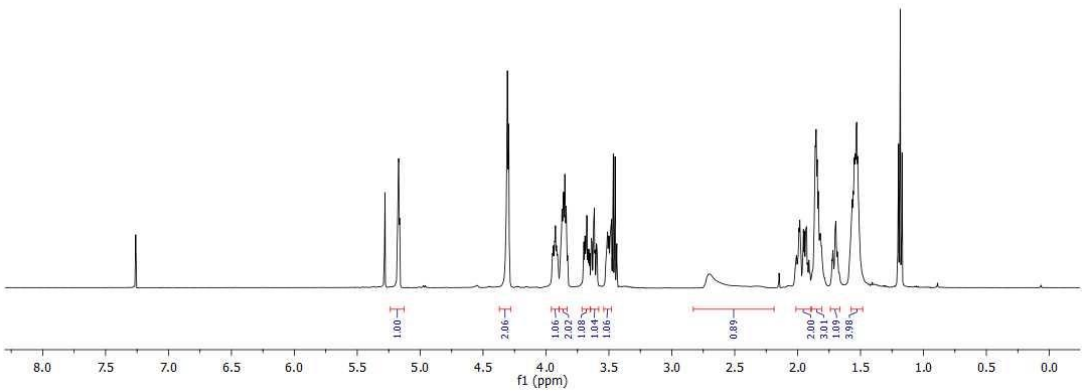

99.2
95.5
95.5
77.4
77.4
77.2
77.2
76.9
76.9
74.8
74.8
63.3
63.3
60.5
60.5
51.2
51.2
51.2
38.7
38.7
38.7
32.2
32.2
25.6
25.6
25.4
25.4
14.3
14.3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

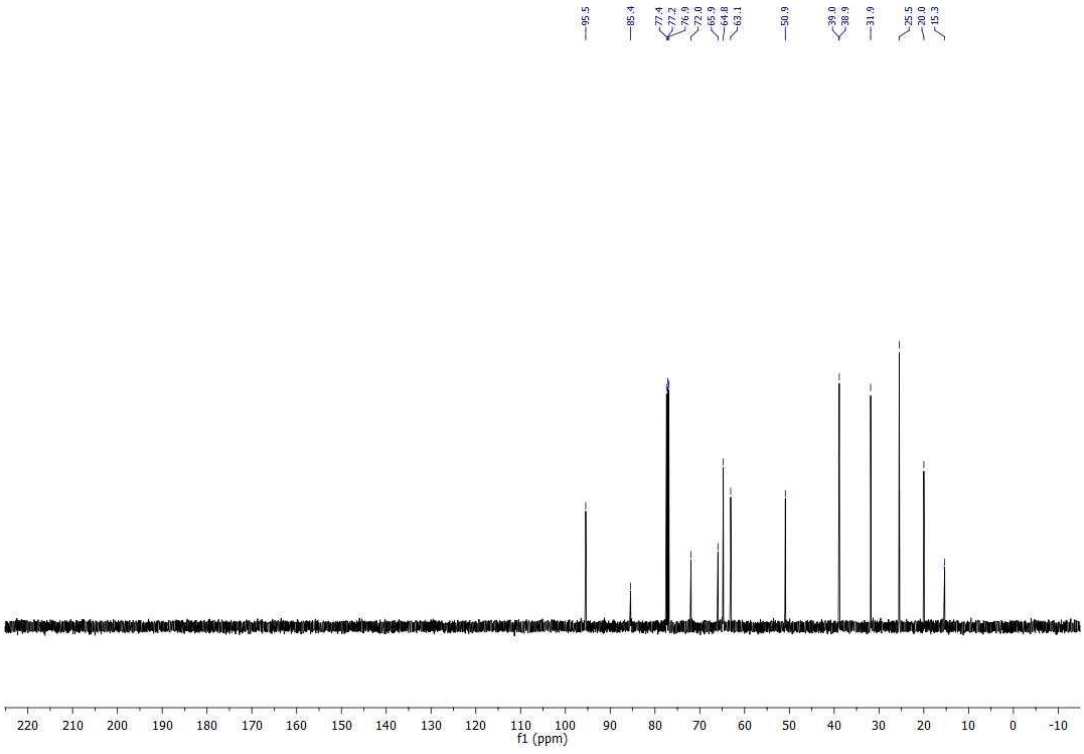

O
O
OH
1.00
2.03
1.04
1.03
1.93
2.04
4.03
3.05
4.15
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

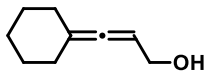

O
O
OH
0.96
2.01
1.00
1.07
0.97
1.05
3.99
0.98
8.10
6.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

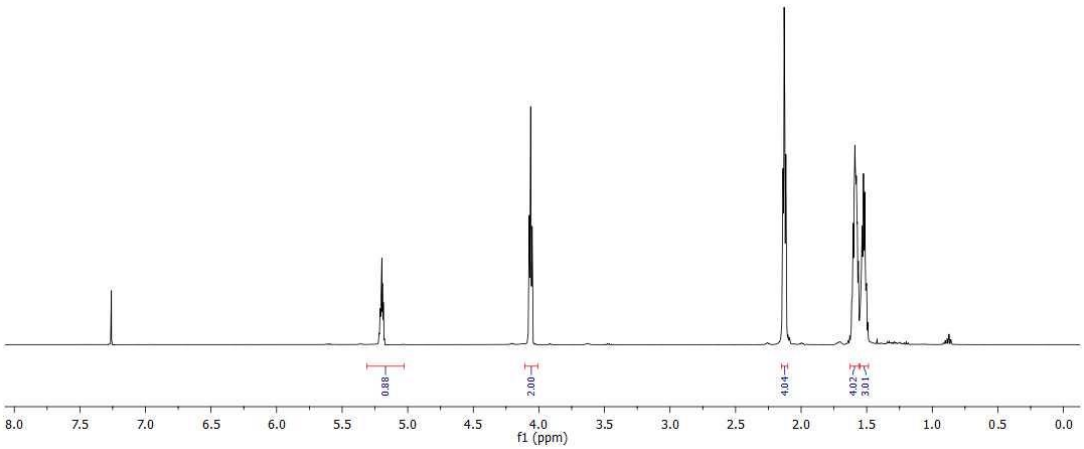

95.3
78.5
77.4
77.2
76.9
66.0
63.4
63.4
51.2
38.0
37.7
37.5
35.6
35.5
35.4
32.4
32.1
32.0
31.7
27.1
26.9
25.7
20.2
20.2
15.4
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

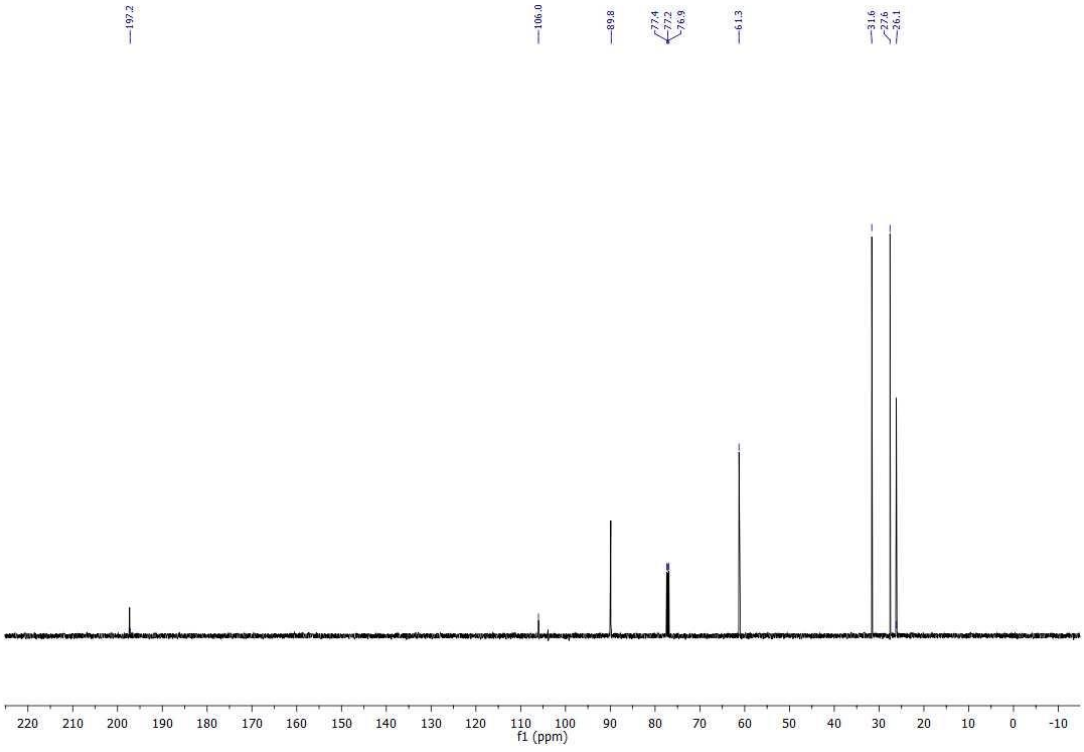

O
O
O
OH

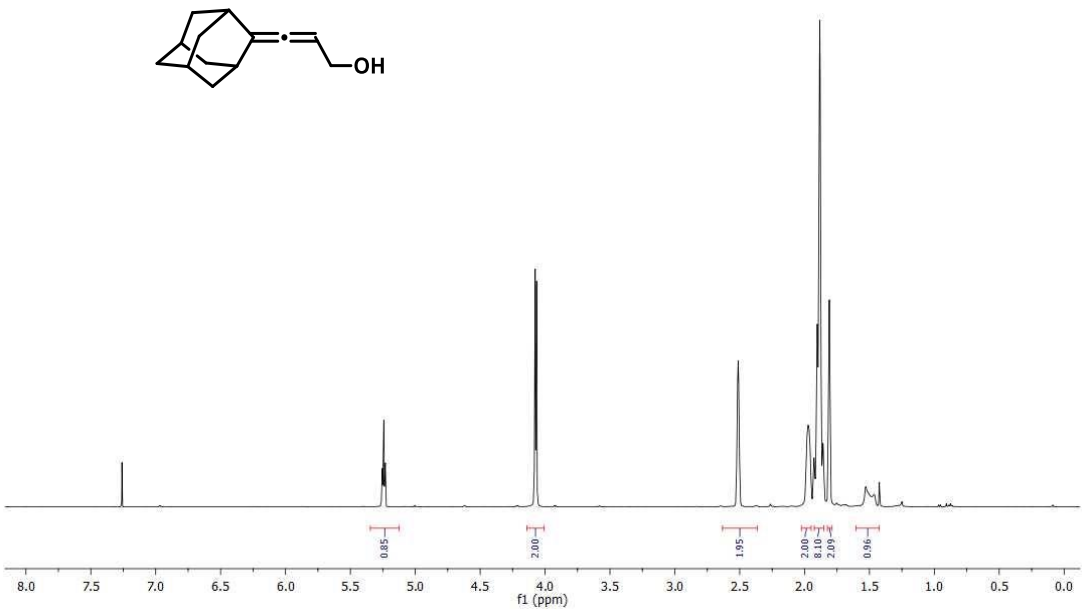

1.00
2.06
1.06
2.02
1.08
1.04
1.06
0.89
2.00
3.01
1.09
3.98
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

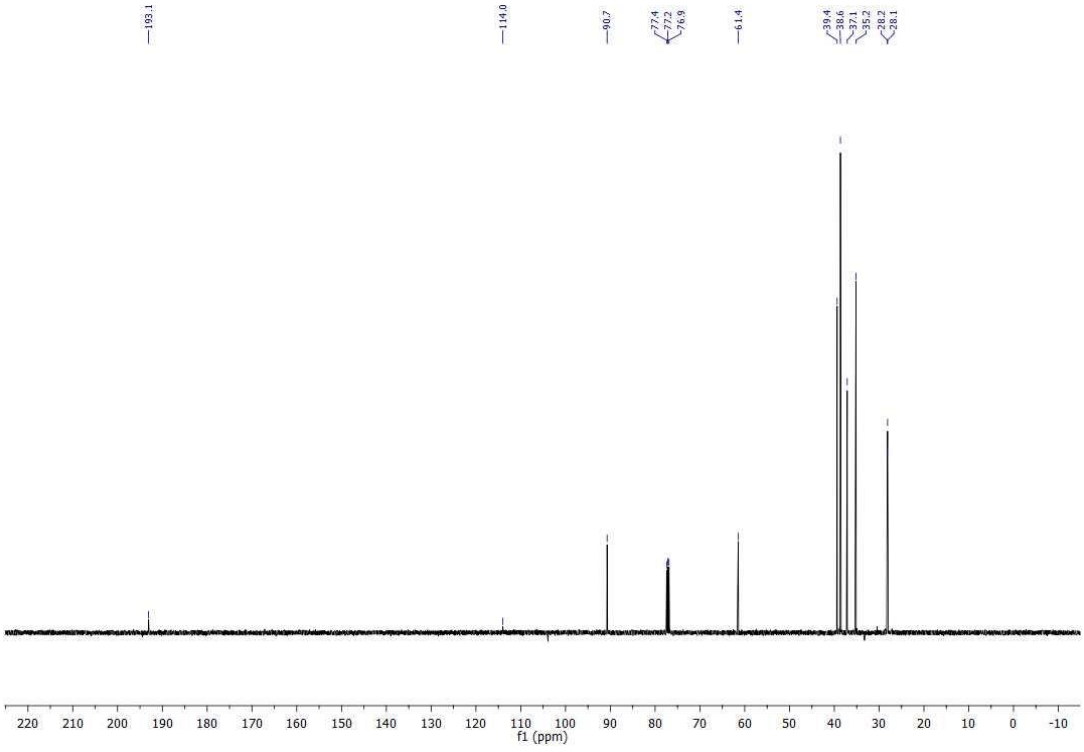

95.5
95.4
77.4
77.2
76.9
72.0
65.9
64.8
63.1
50.9
39.0
38.9
31.9
25.5
20.0
15.3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

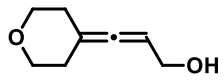

OH

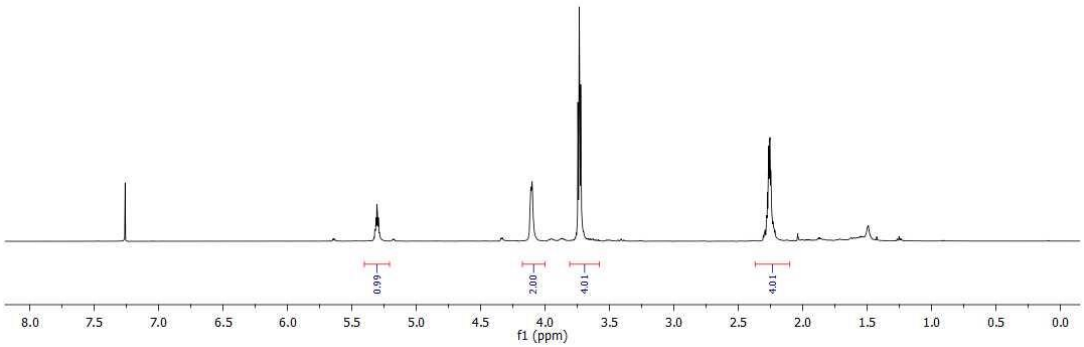

0.88
2.00
4.04
4.02
3.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

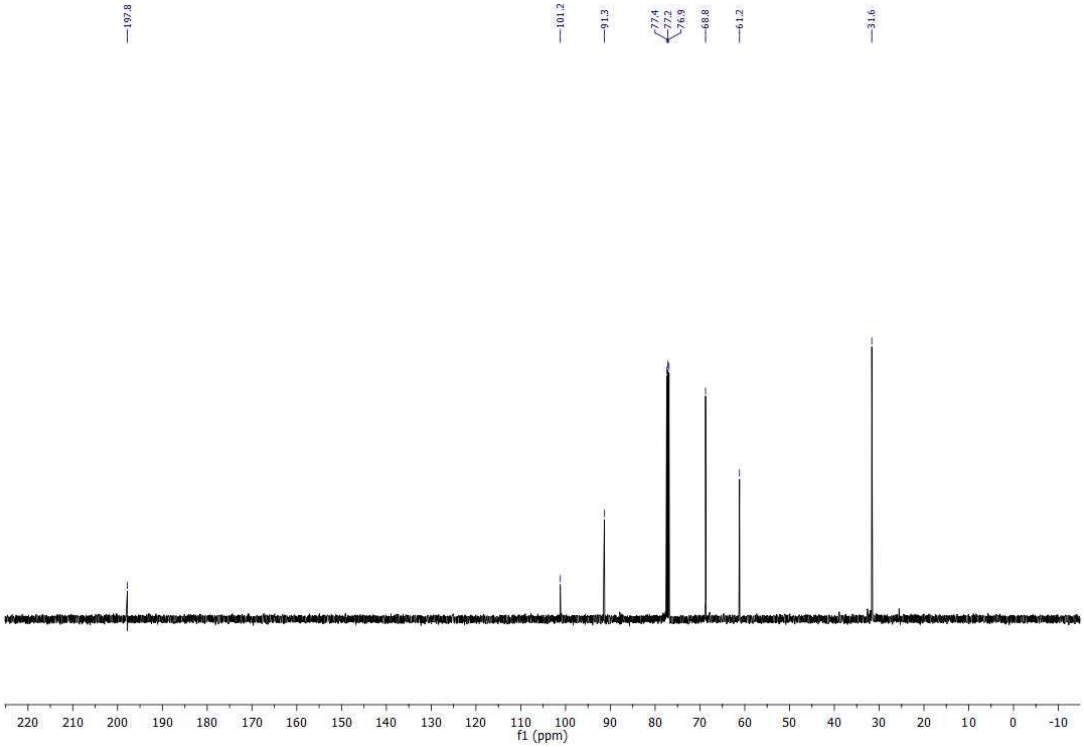

197.2
106.0
89.8
77.4
77.2
76.9
61.3
31.6
27.6
26.1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

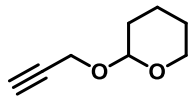

OH
0.85
2.00
1.95
2.00
8.10
2.09
0.96
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

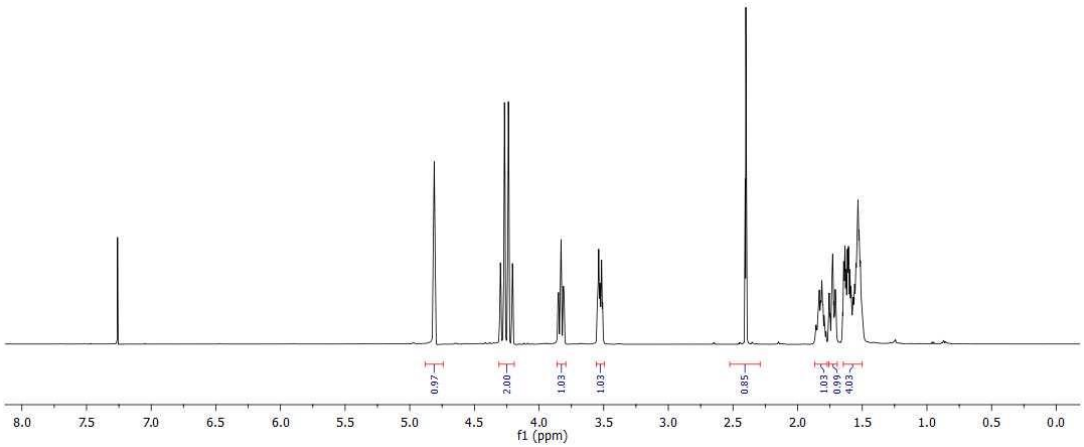

193.1
114.0
90.7
77.4
77.2
76.9
61.4
39.4
38.6
37.1
35.2
28.2
28.1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

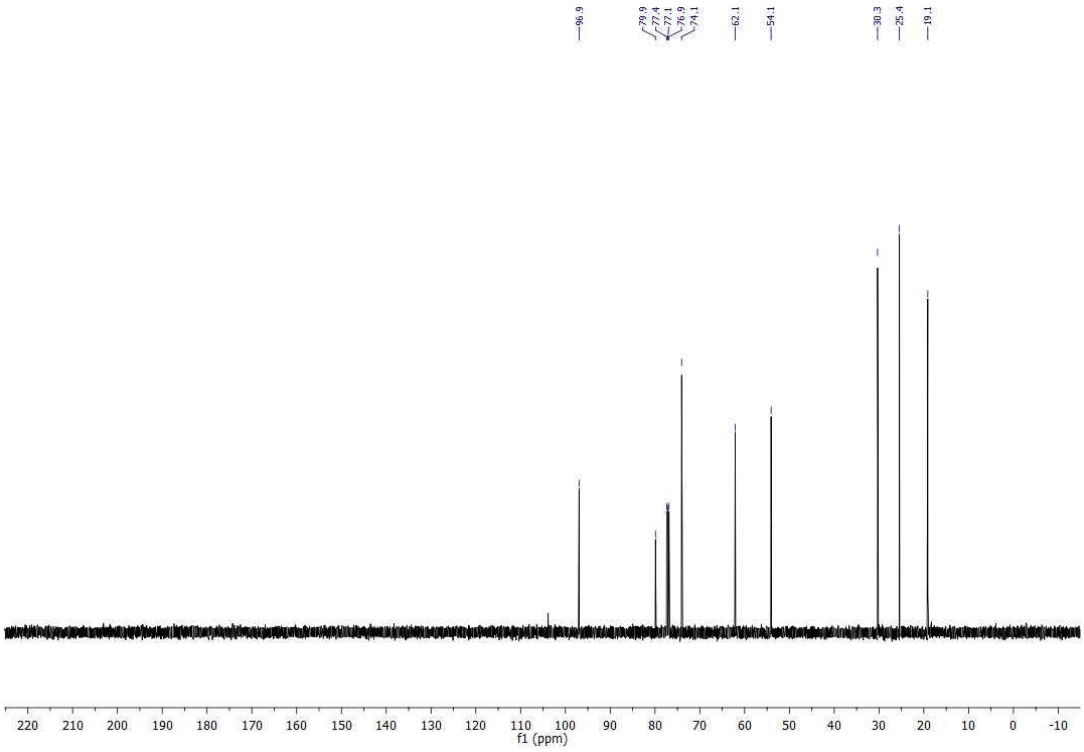

O
OH

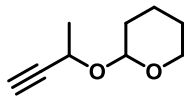

0.99
2.00
4.01
4.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

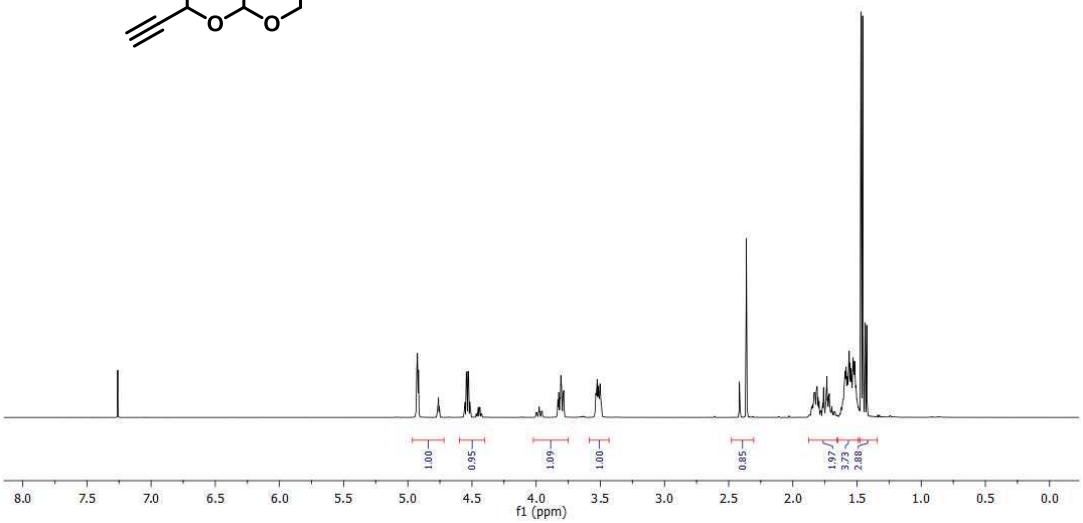

197.8
101.2
91.3
77.4
77.2
76.9
68.8
61.2
31.6
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

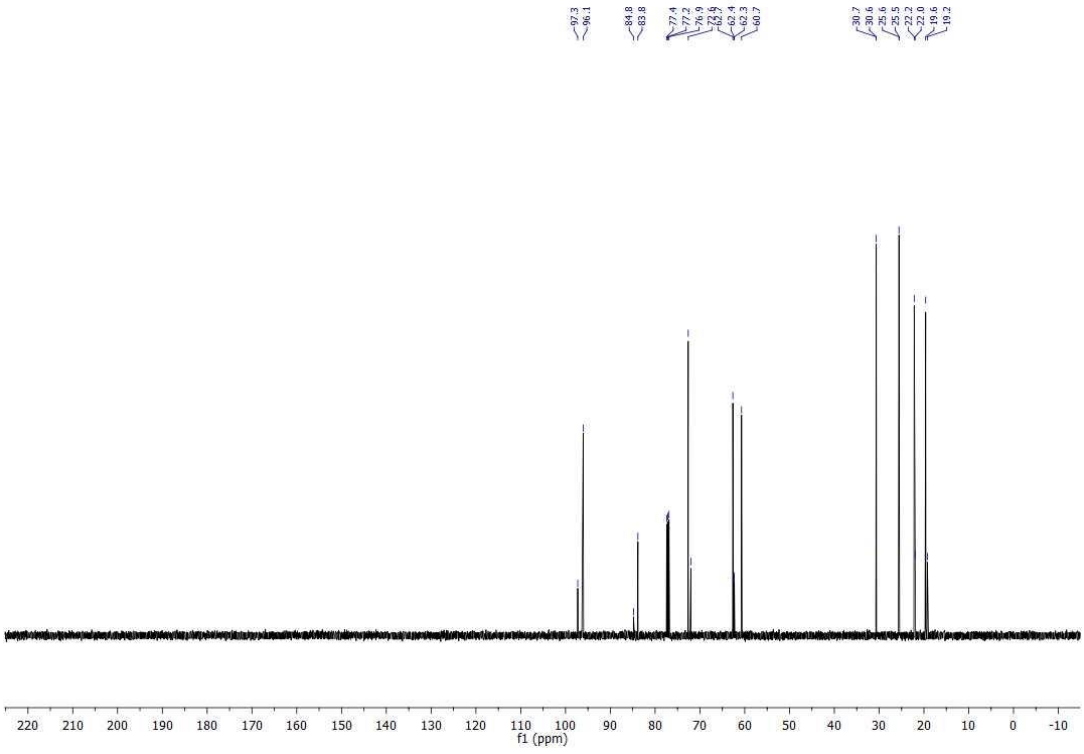


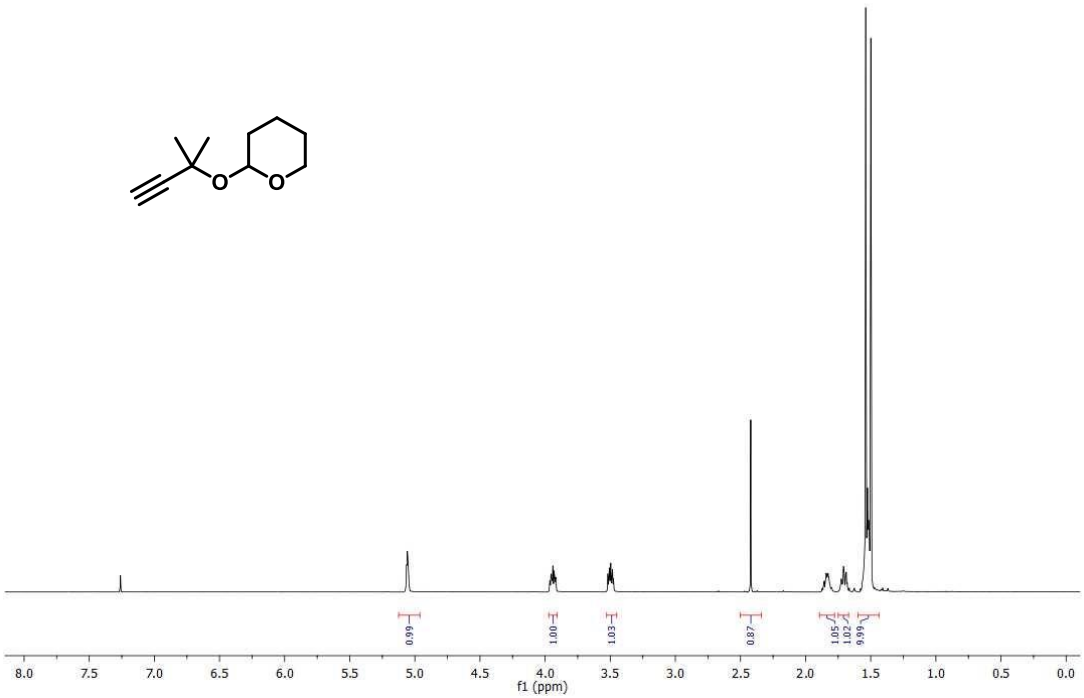

0.97
2.00
1.03
1.03
0.85
1.03
0.99
4.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

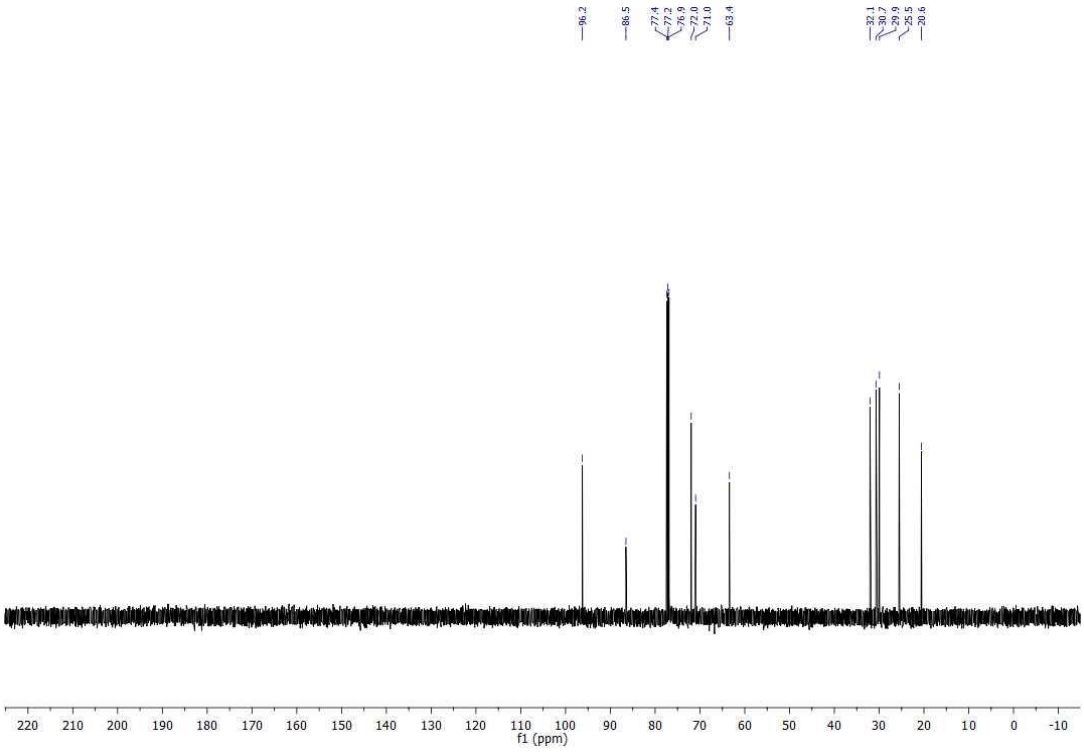

96.9
79.9
77.4
77.1
76.9
74.1
62.1
54.1
30.3
25.4
19.1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

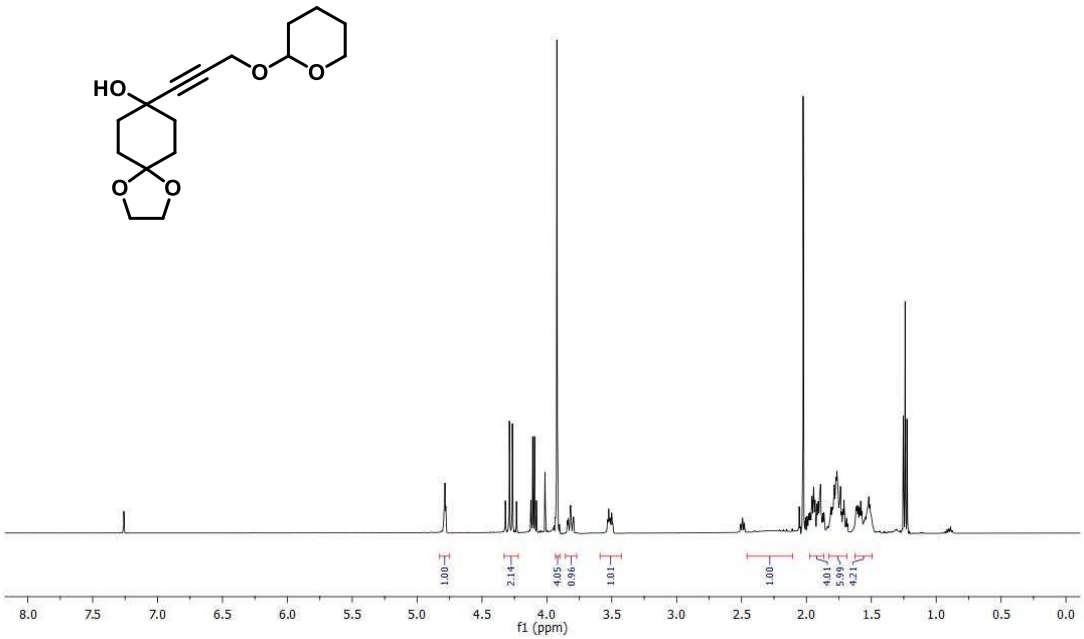


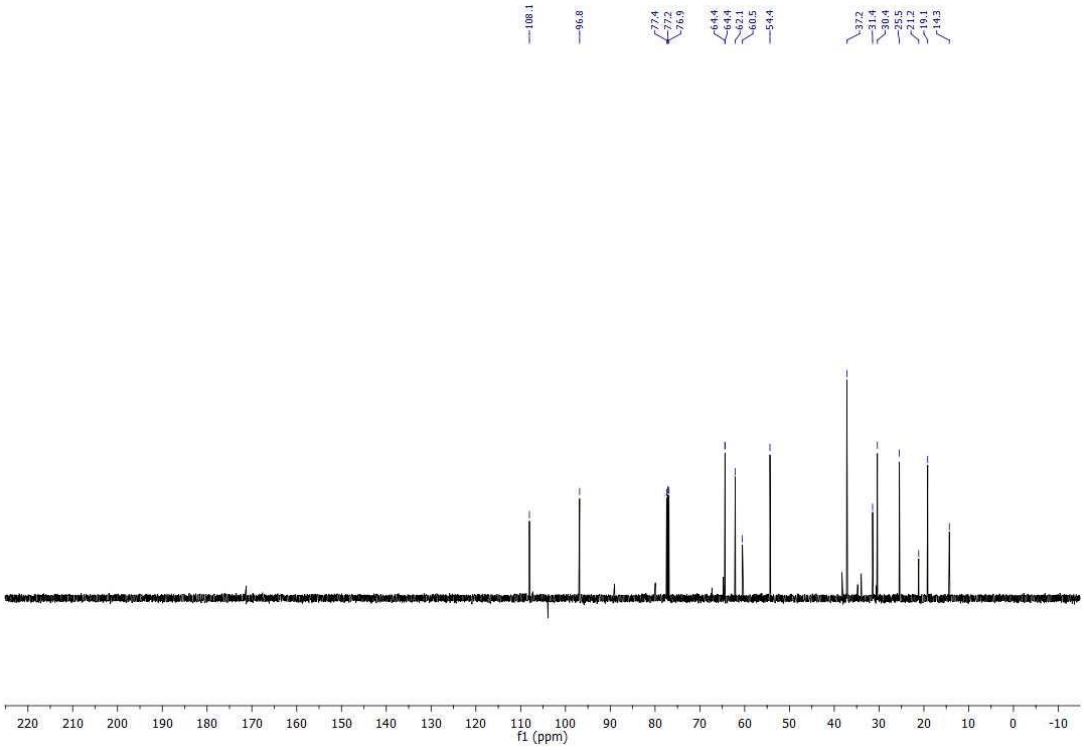

1.00
0.95
1.09
1.00
0.85
1.97
3.73
2.88
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

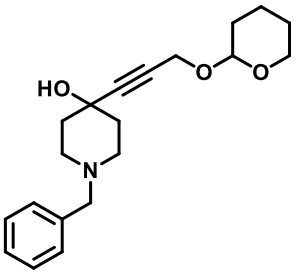

97.3
96.1
84.8
83.8
77.4
77.2
76.9
72.6
62.7
62.4
62.3
60.7
30.7
30.6
25.6
25.5
22.2
22.0
19.6
19.2
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

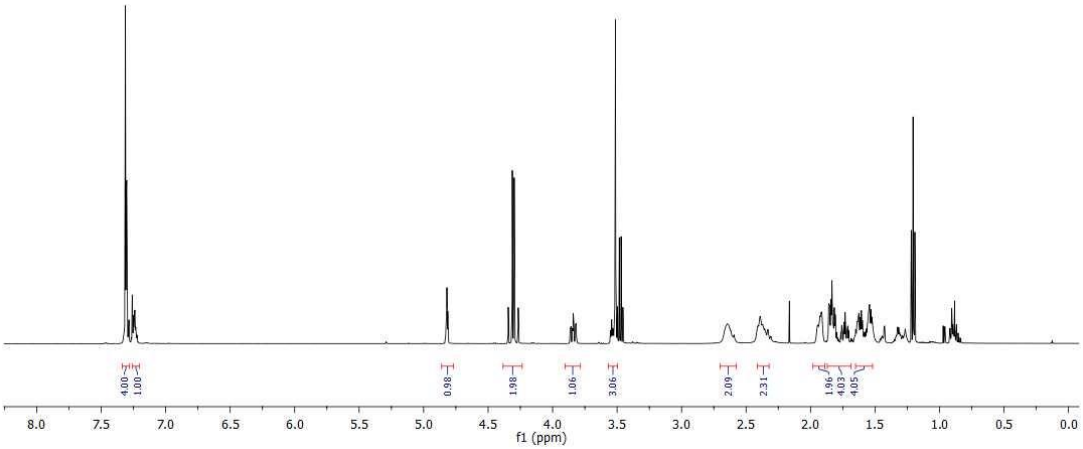

0.99
1.00
1.03
0.87
1.05
1.02
9.99
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


96.2
86.5
77.4
77.2
76.9
72.0
71.0
63.4
32.1
30.7
30.9
25.5
20.6
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

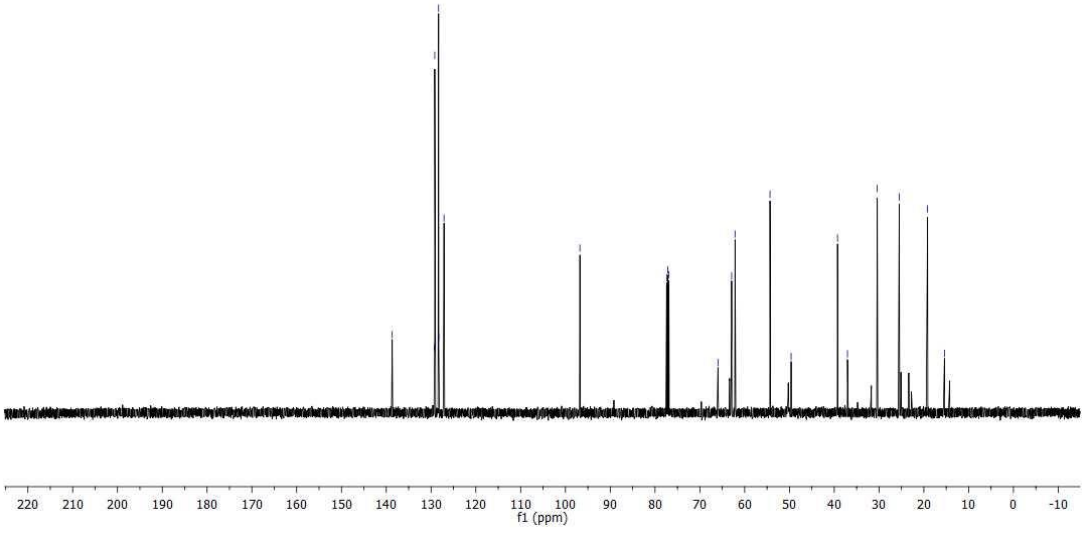

HO
O
O
O
O
1.00
2.14
4.05
0.96
1.01
1.00
4.01
5.99
4.21
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

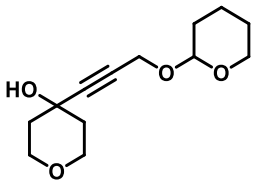

108.1
96.8
77.4
77.2
76.9
64.4
64.4
62.1
60.5
54.4
37.2
31.4
30.4
25.5
21.2
19.1
14.3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

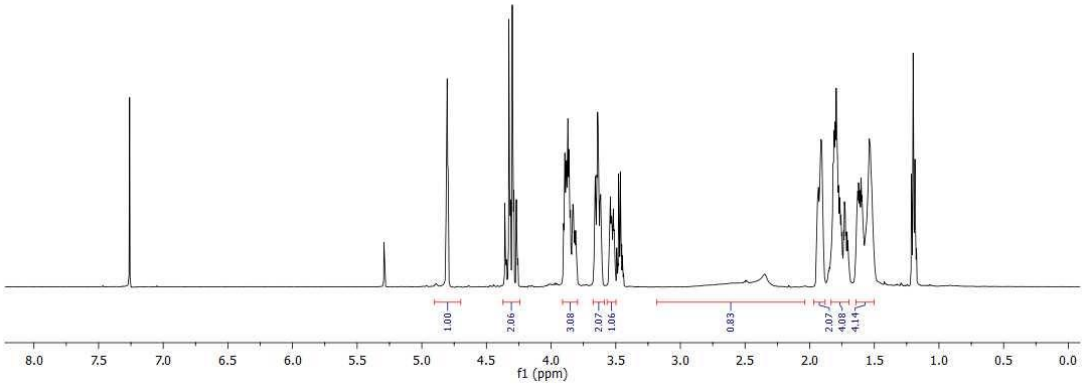

HO
O
O
N

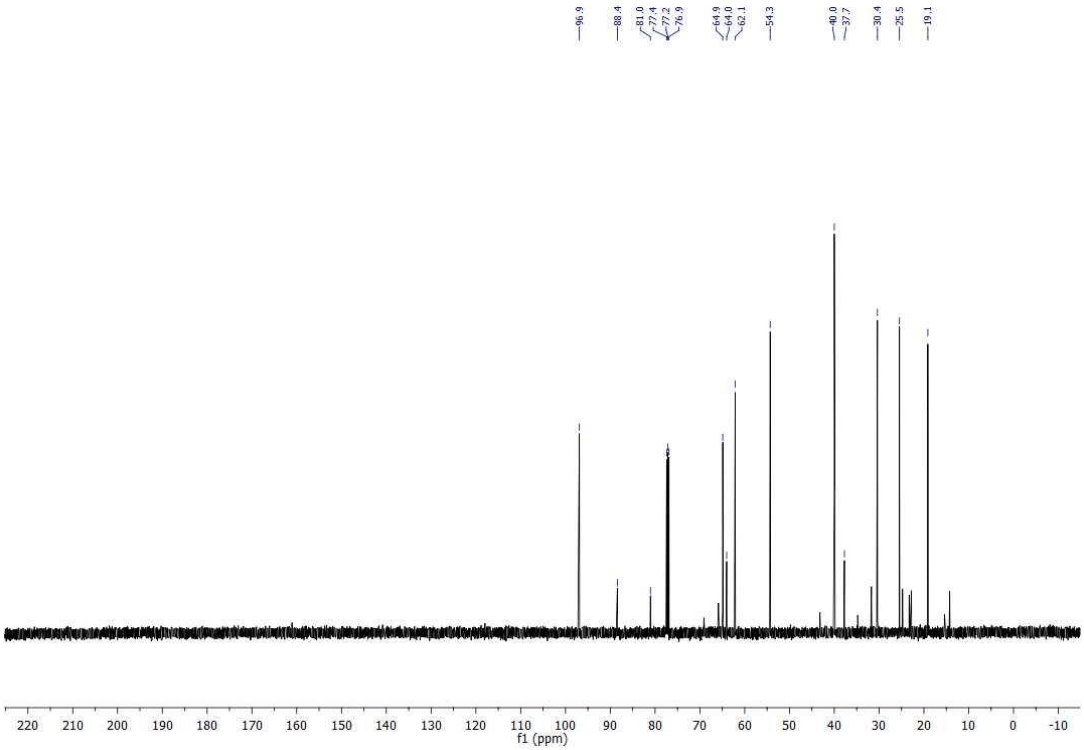

4.00
1.00
0.98
1.98
1.06
3.06
2.09
2.31
1.96
4.03
4.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


138.7
129.3
129.2
128.3
128.3
127.1
96.8
77.4
77.2
76.9
66.0
62.9
62.1
54.3
49.6
39.3
37.0
30.4
25.5
19.2
15.4


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


HO
O
O
O


1.00
2.06
3.08
2.07
1.06
0.83
2.07
4.08
4.14
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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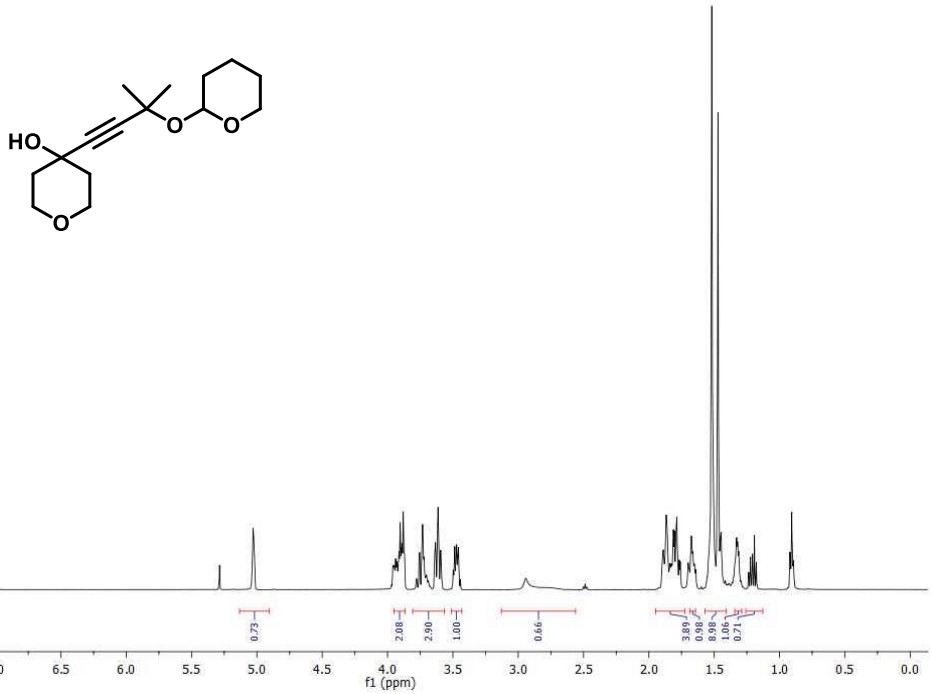
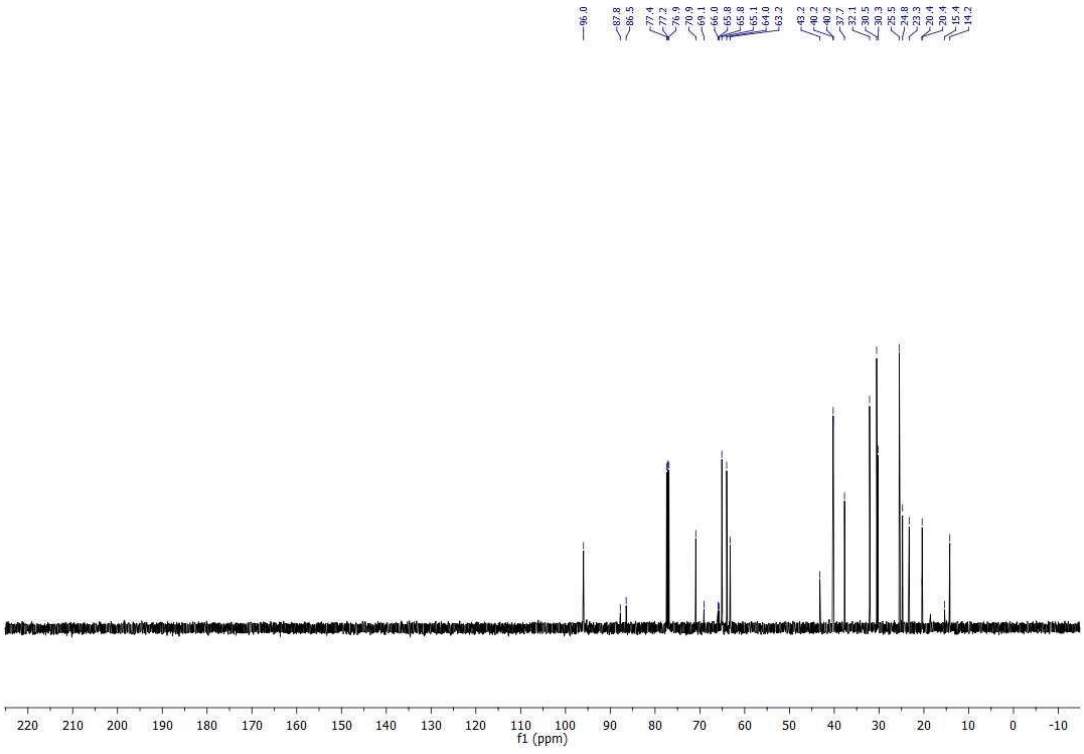
88.4
81.0
77.4
77.2
76.9
64.9
64.0
62.1
54.3
40.0
37.7
30.4
25.5
19.1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


HO
O
O
O
0.73
2.08
2.90
1.00
0.66
3.89
0.98
8.98
1.06
0.71
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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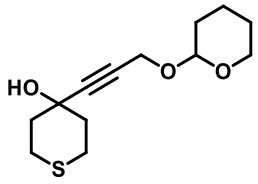
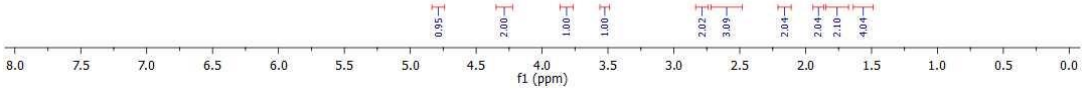
87.8
86.5
77.4
77.2
76.9
70.9
69.1
66.0
65.8
65.8
65.1
64.0
63.2
48.2
40.2
40.2
37.7
32.1
30.5
30.3
25.5
24.8
23.3
20.4
20.4
15.4
14.2
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


HO
O
O
S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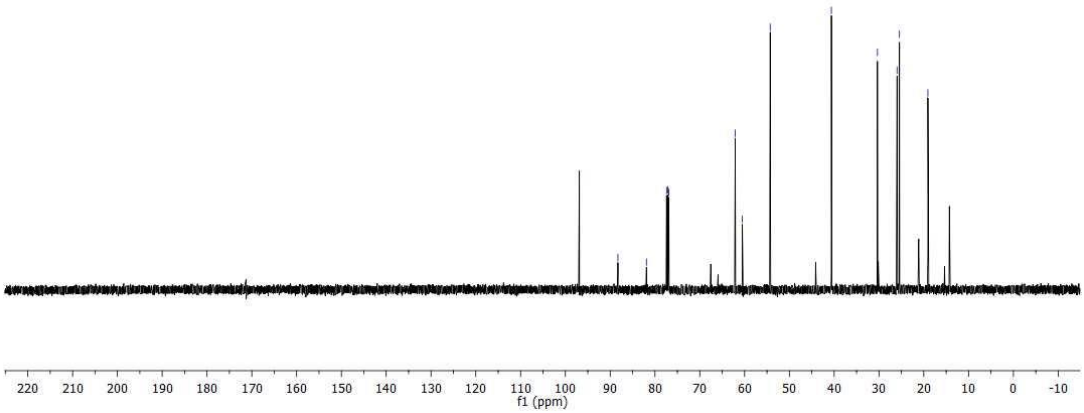
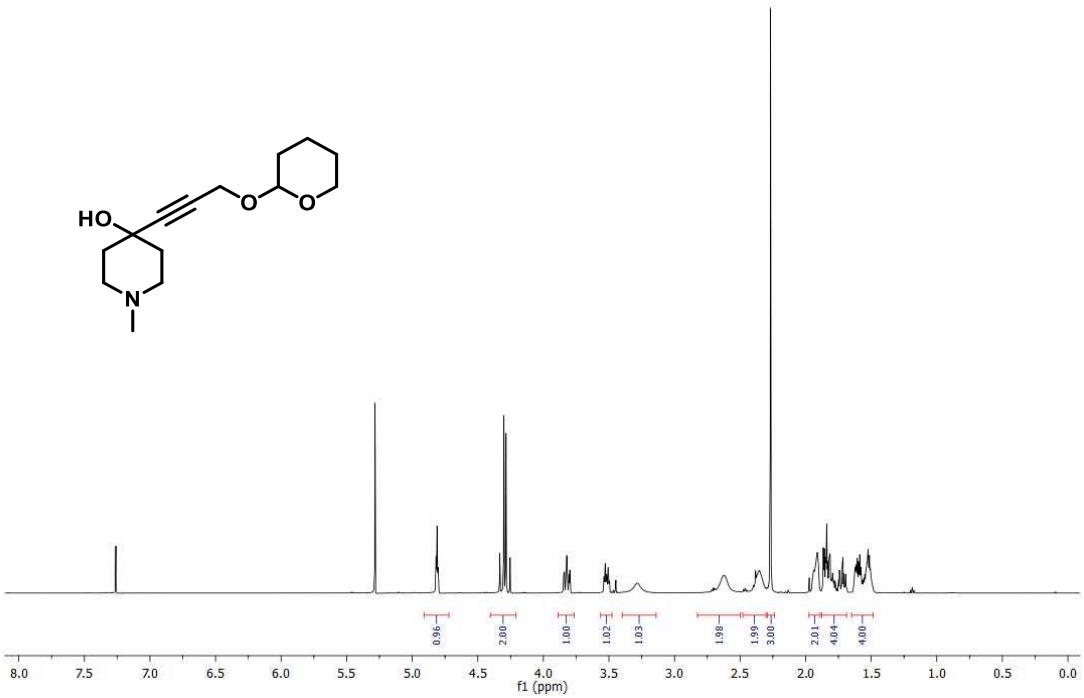
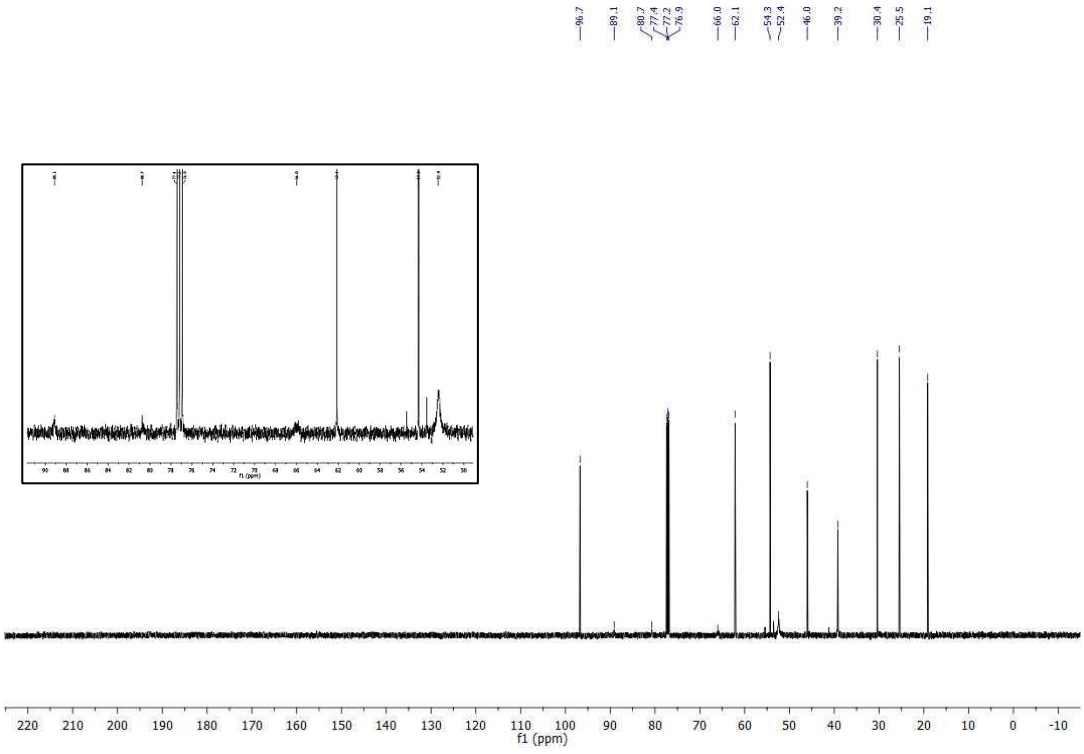
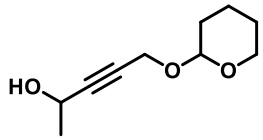
2.00
1.00
1.00
2.02
3.09
2.04
2.04
2.10
4.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

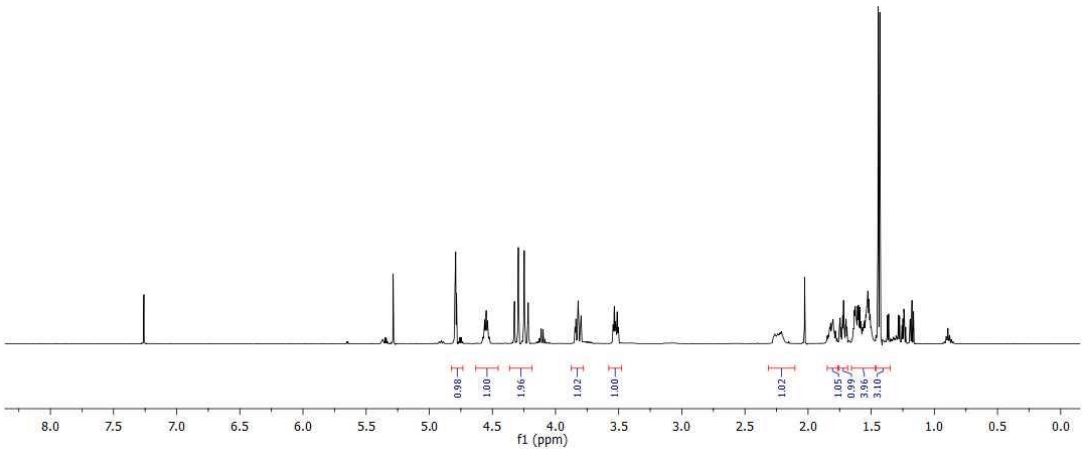

96.9
88.3
81.9
77.4
77.2
76.9
62.1
60.5
54.3
40.6
30.3
26.0
25.4
19.1

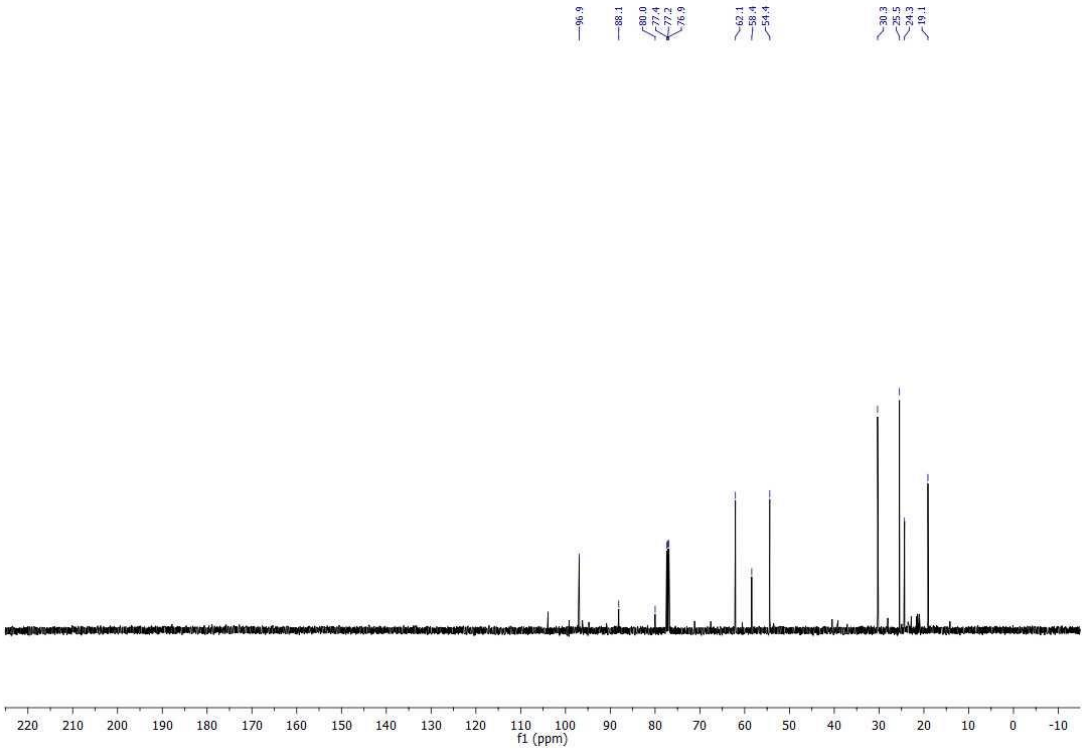

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


HO
O
O
N
0.96
2.00
1.00
1.02
1.03
1.98
1.99
3.00
2.01
4.04
4.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


96.7
89.1
80.7
77.4
77.2
76.9
66.0
62.1
54.3
52.4
46.0
39.2
30.4
25.5
19.1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


HO
O
O


0.98
1.00
1.96
1.02
1.00
1.02
1.05
0.99
3.96
3.10
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


96.9
88.1
80.0
77.4
77.2
76.9
62.1
58.4
54.4
30.3
25.5
24.3
19.1
220
210
200
190
180
170
160
150
140
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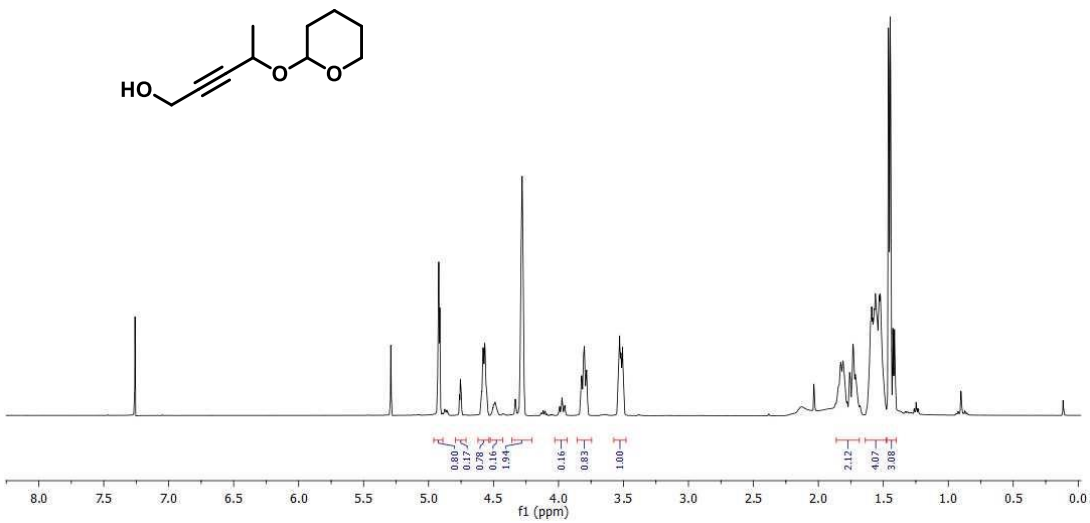
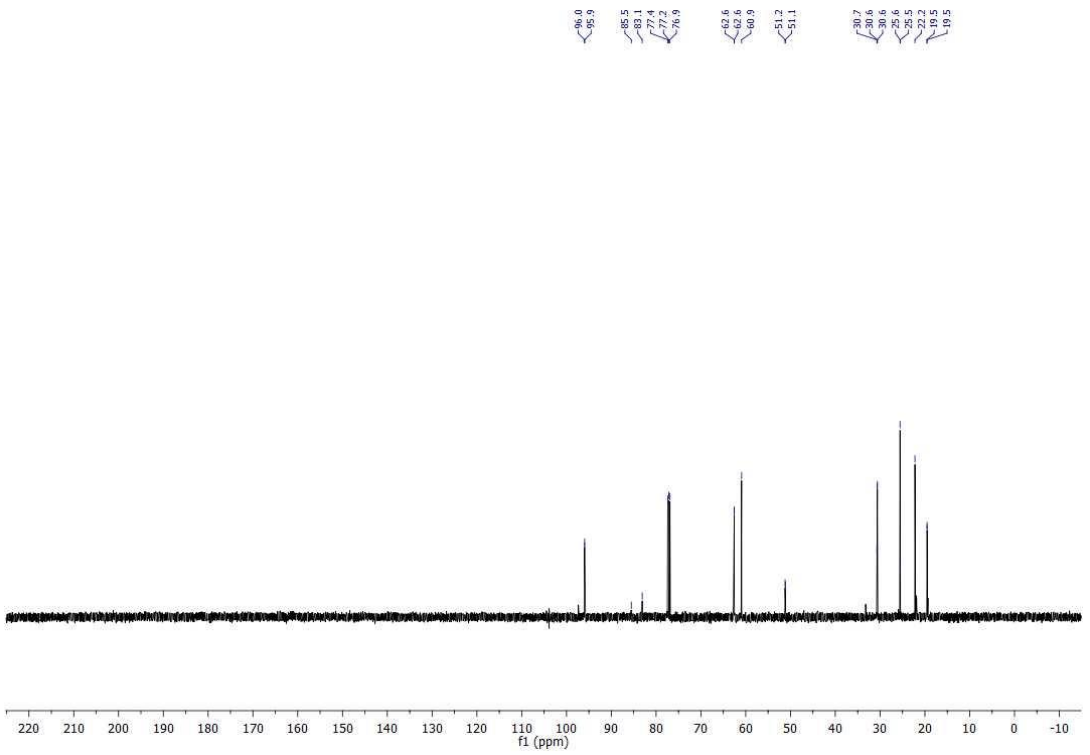
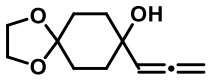
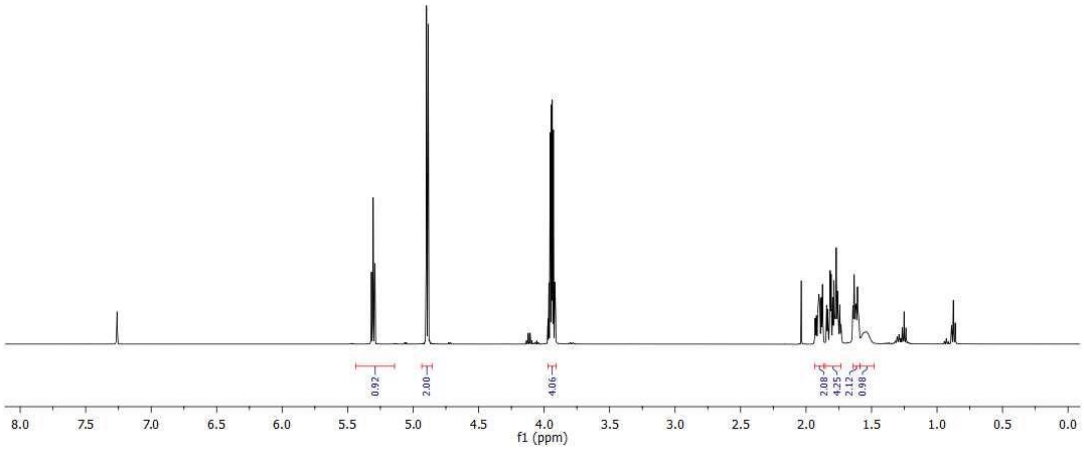
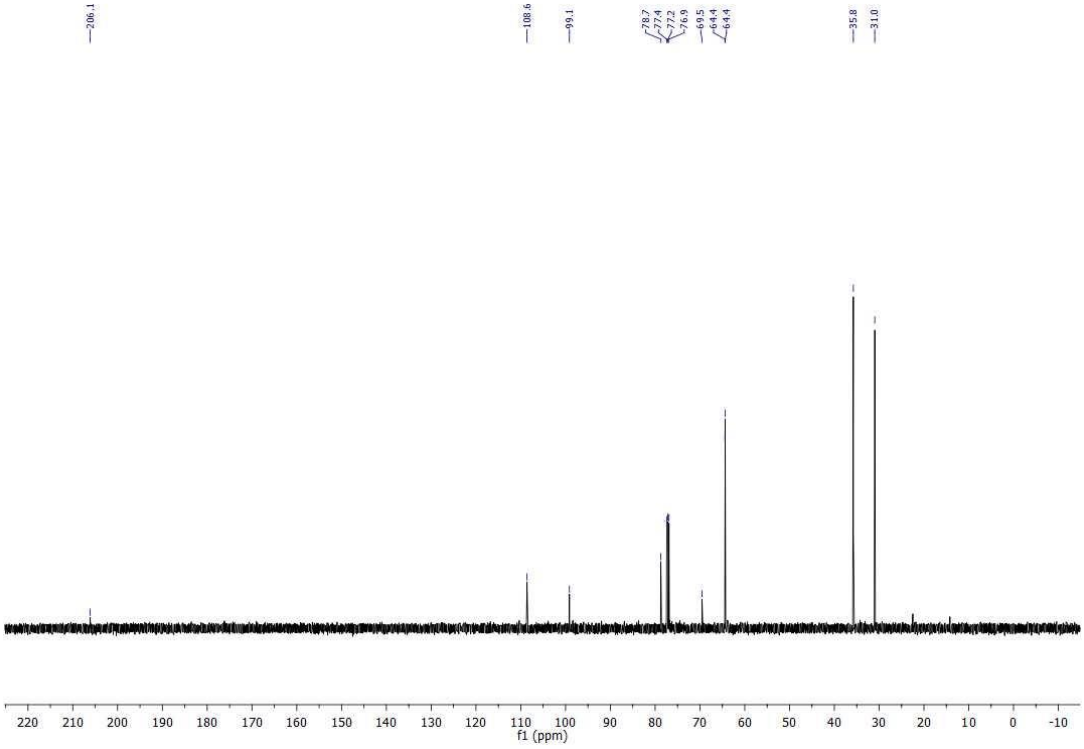
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

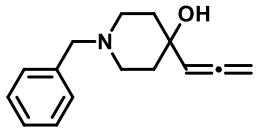

HO
O
O
0.80
0.17
0.78
0.16
1.94
0.16
0.83
1.00
2.12
4.07
3.08
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

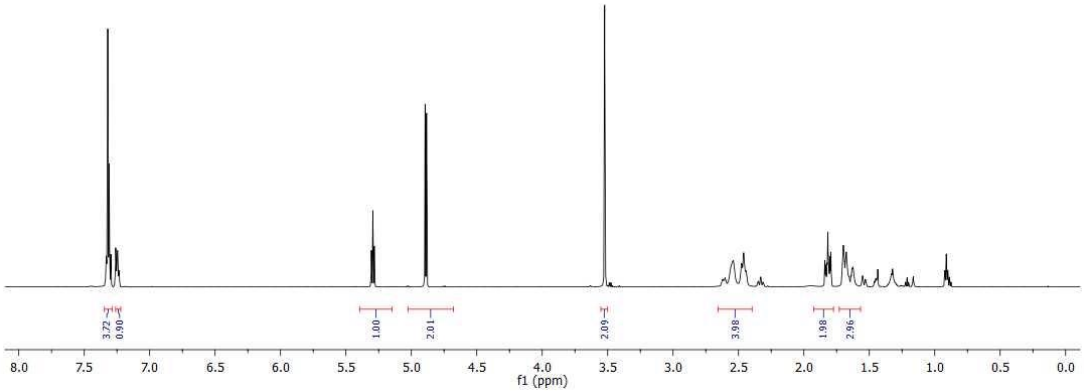

96.0
95.9
85.5
83.1
77.4
77.2
76.9
62.6
62.6
60.9
51.2
51.1
30.7
30.6
30.6
25.6
25.5
22.2
19.5
19.5
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

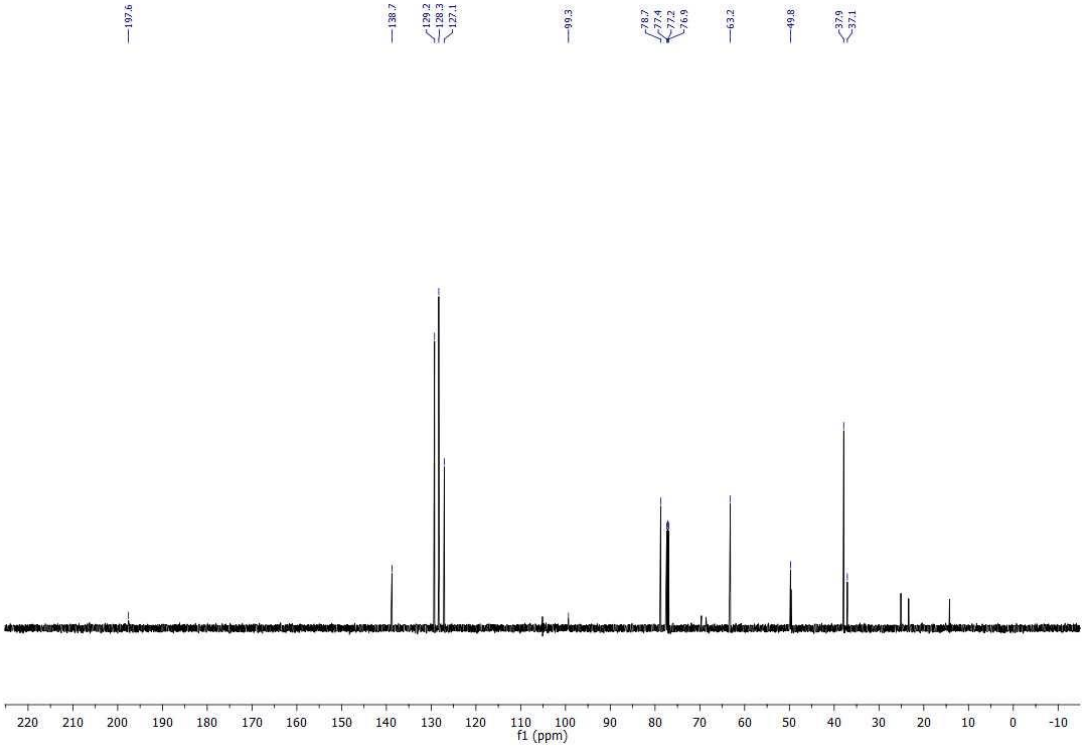

O
O
OH

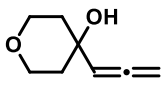

0.92
2.00
4.06
2.08
4.25
2.12
0.98
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

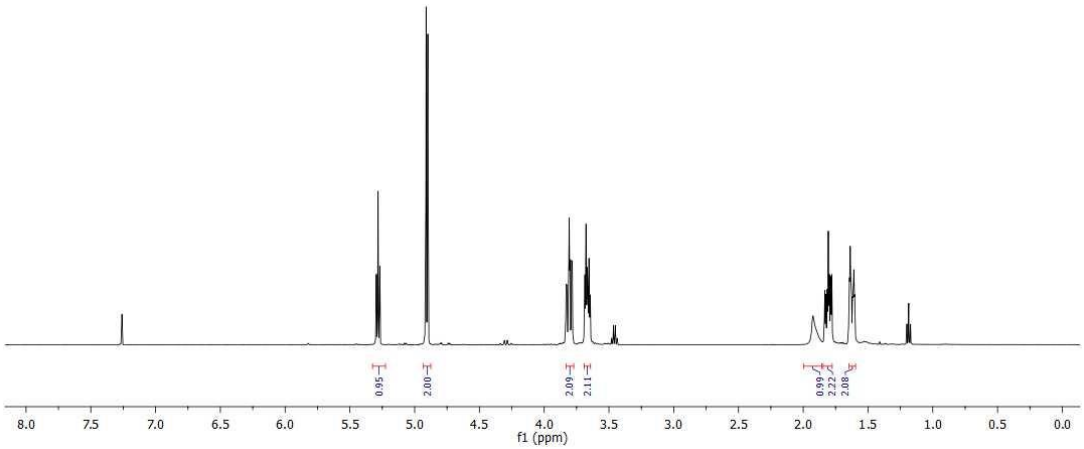

206.1
108.6
99.1
78.7
77.4
77.2
76.9
69.5
64.4
64.4
35.8
31.0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

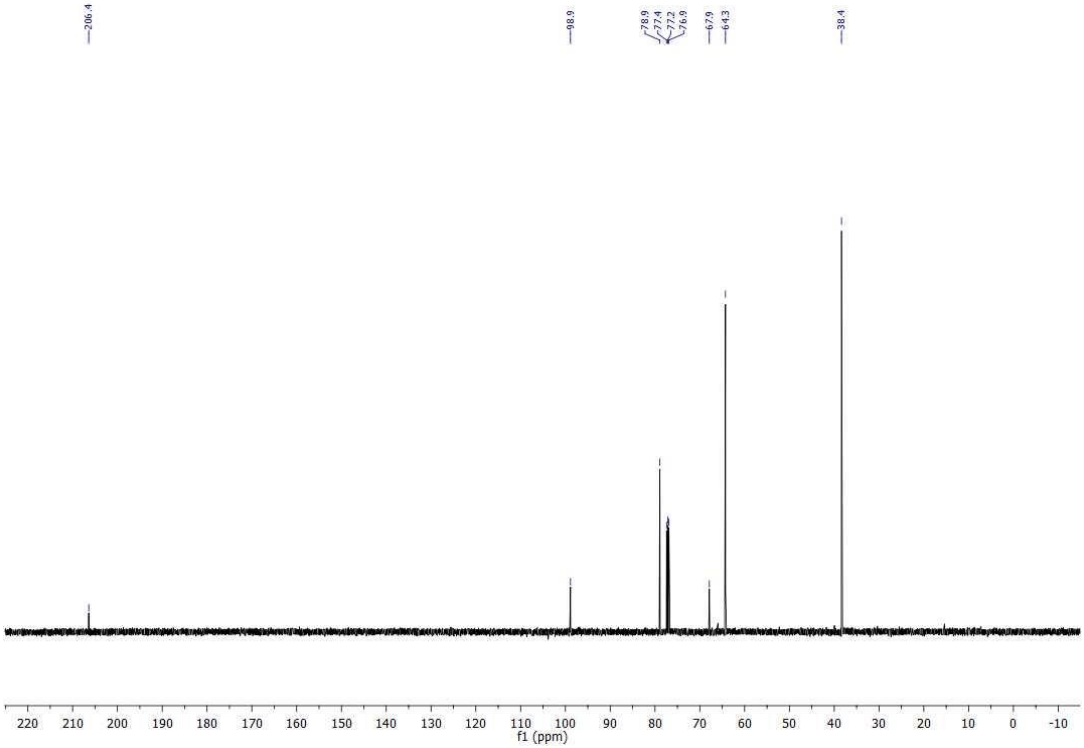

OH
N

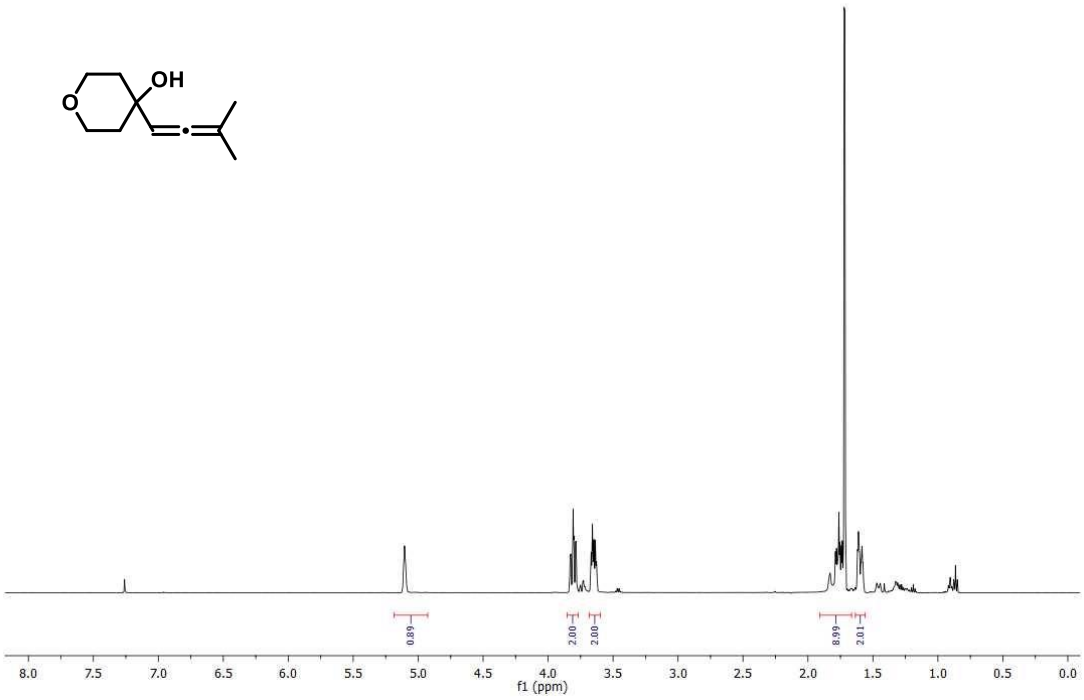

3.72
0.90
1.00
2.01
2.09
3.98
1.98
2.96
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

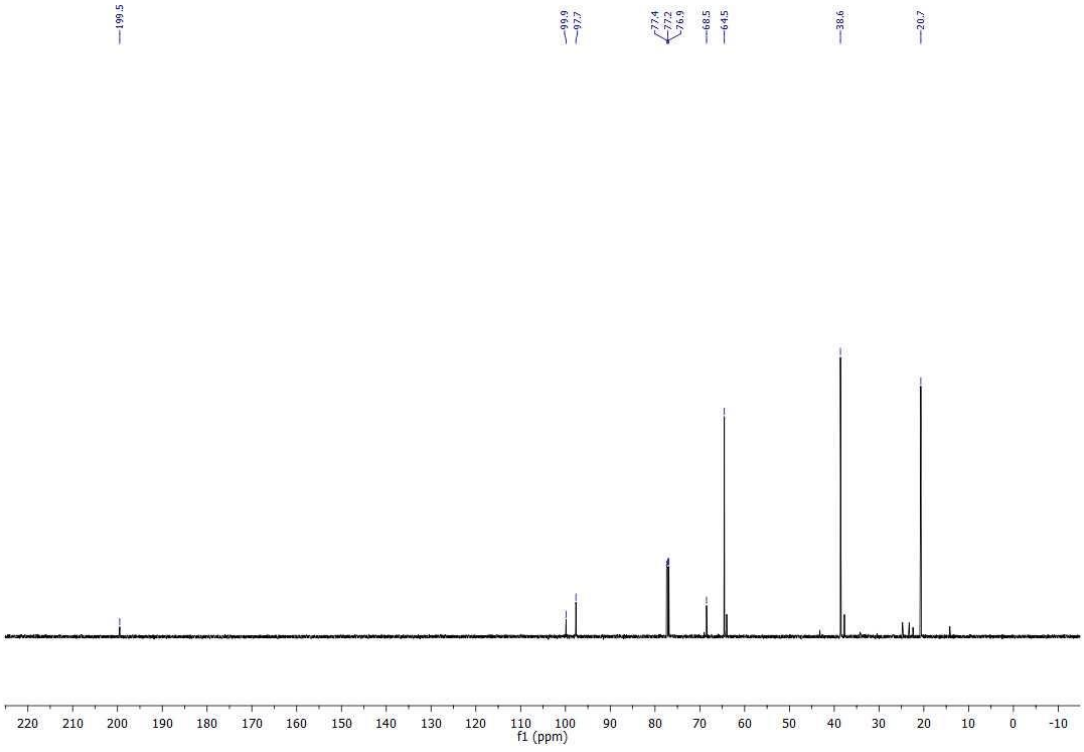

197.6
138.7
129.2
128.3
127.1
99.3
78.7
77.4
77.2
76.9
63.2
49.8
37.9
37.1
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

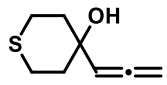

OH
O

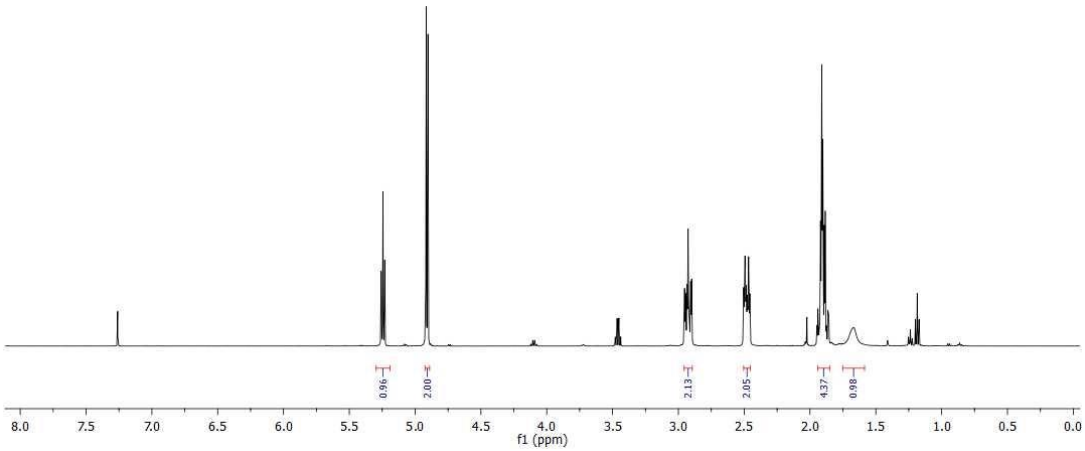

0.95
2.00
2.09
2.11
0.99
2.22
2.08
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

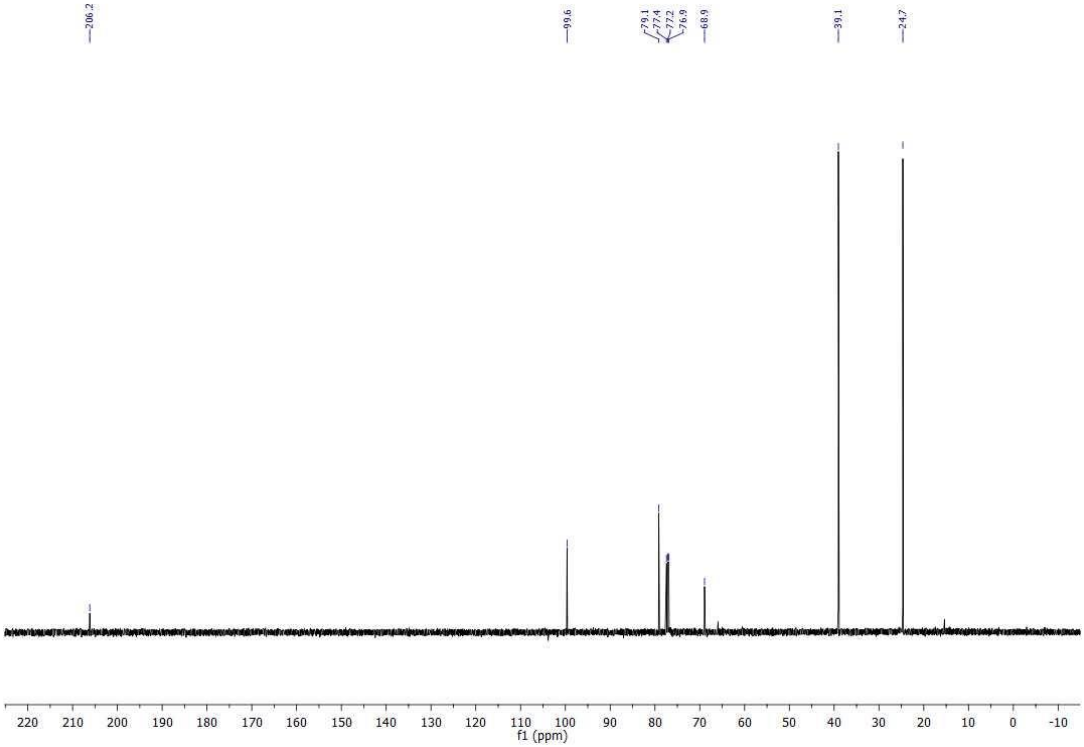

206.4
98.9
78.9
77.4
77.2
76.9
67.9
64.3
38.4
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

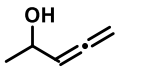

OH
O
0.89
2.00
2.00
8.99
2.01
f1 (ppm)

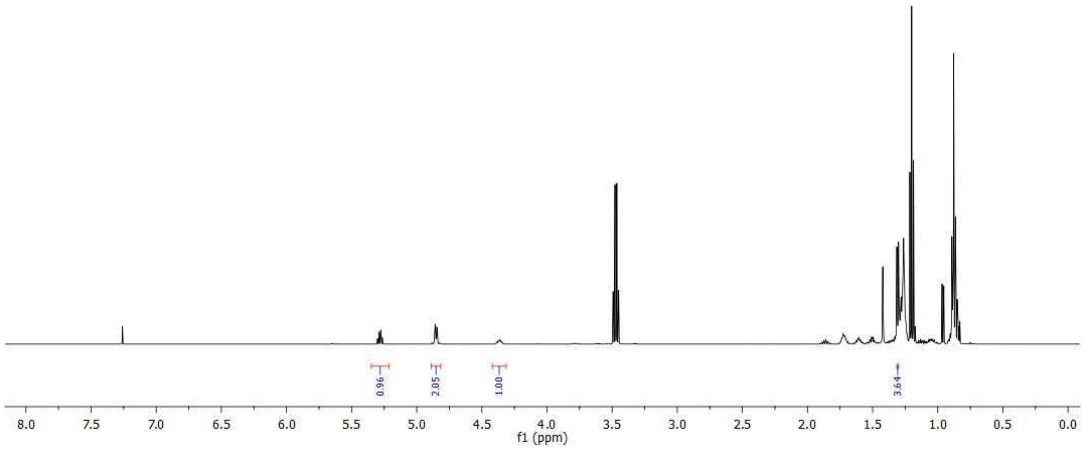

199.5
99.9
97.7
77.4
77.2
76.9
68.5
64.5
38.6
20.7
f1 (ppm)

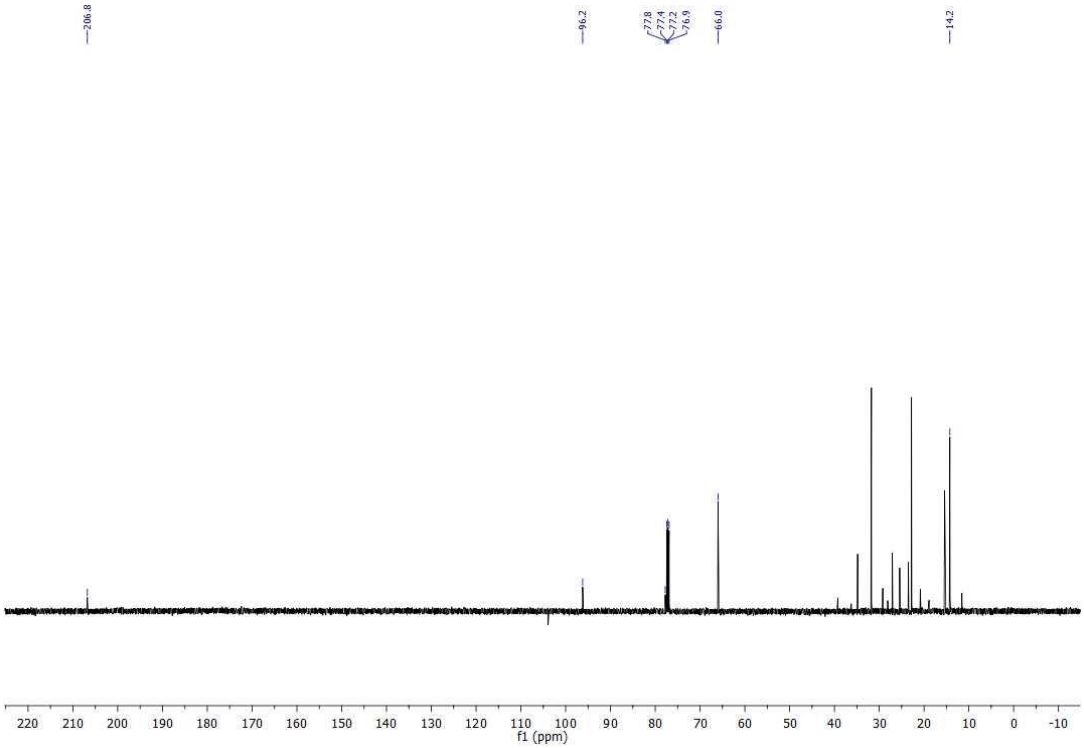

OH
S

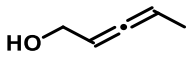

0.96
2.00
2.13
2.05
4.37
0.98
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

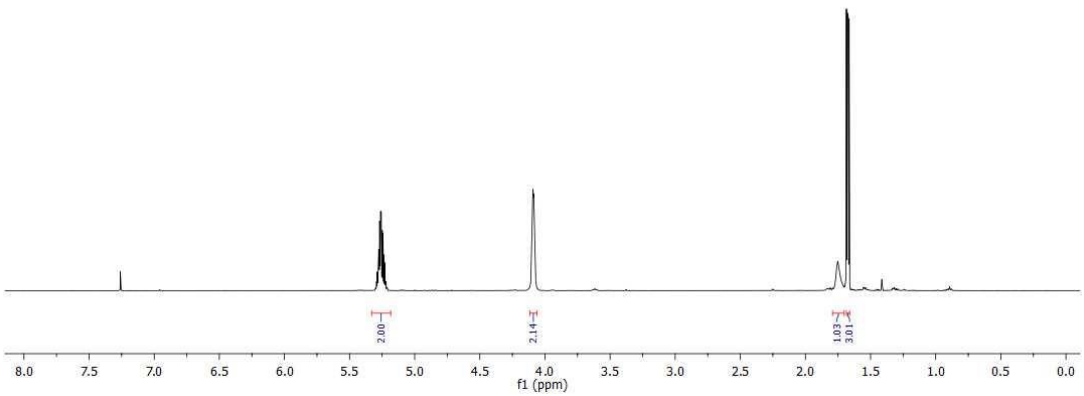

206.2
99.6
79.1
77.4
77.2
76.9
68.9
39.1
24.7
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

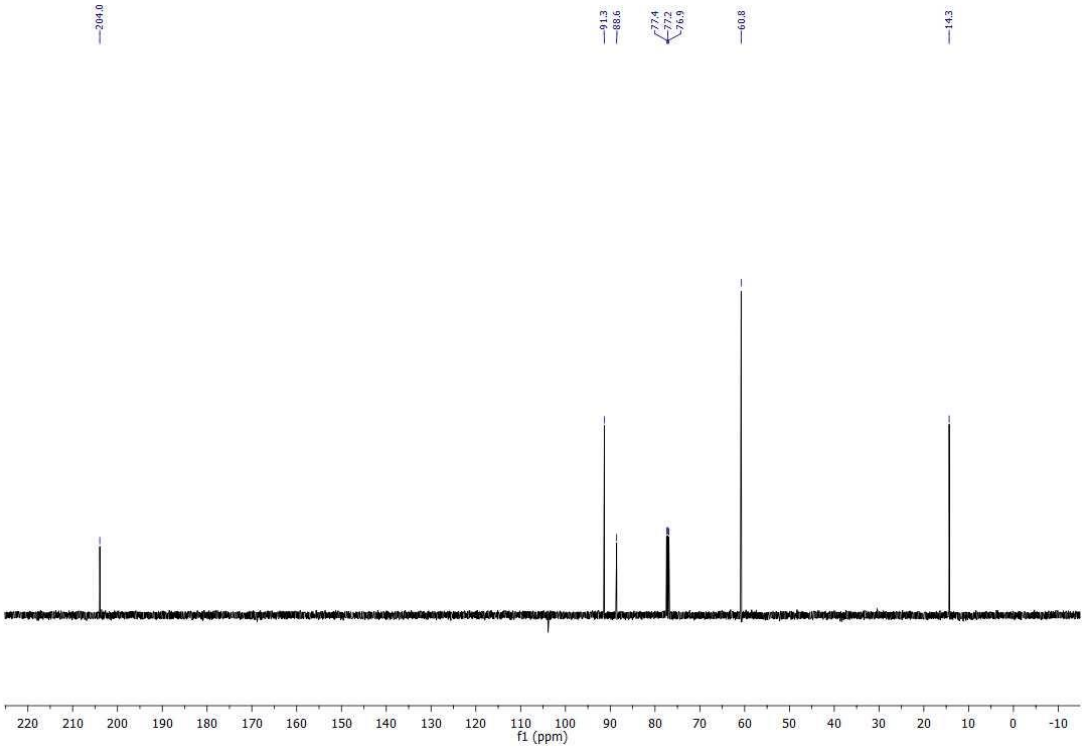

OH

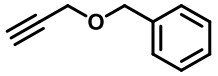

0.96
2.05
1.00
3.64
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

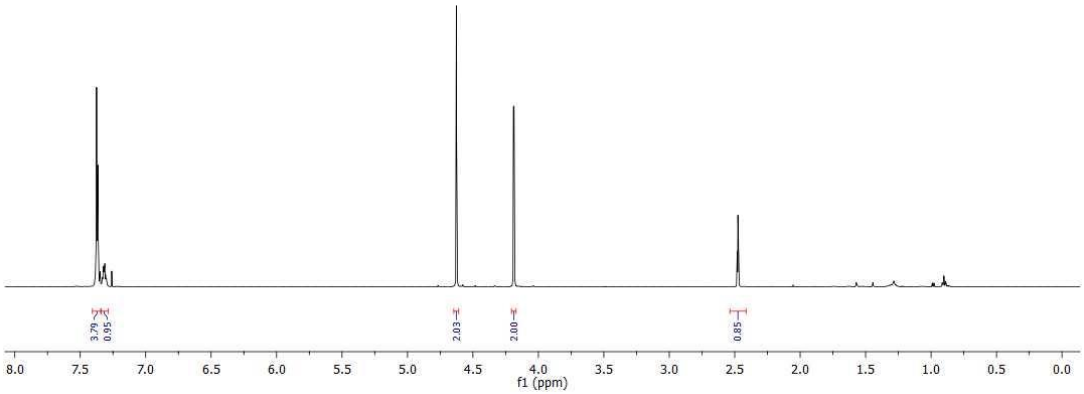

206.8
96.2
77.8
77.4
77.2
76.9
66.0
14.2
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


HO


2.00
2.14
1.03
3.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


204.0
91.3
88.6
77.4
77.2
76.9
60.8
14.3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

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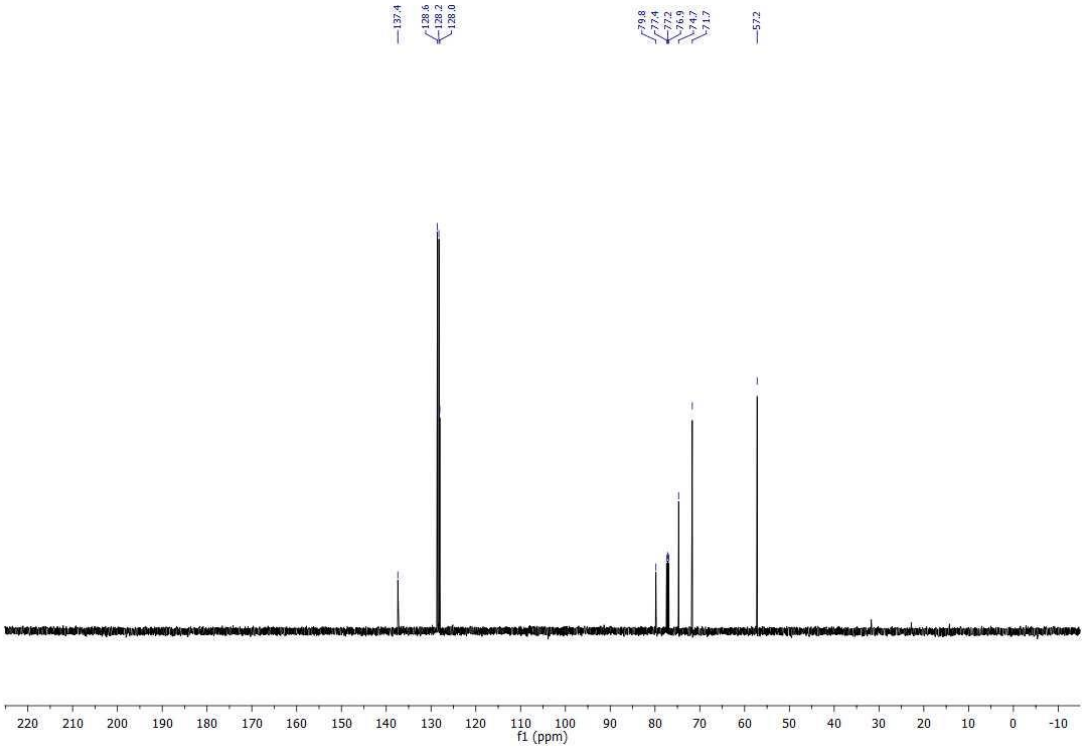
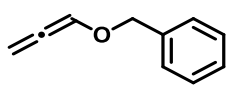
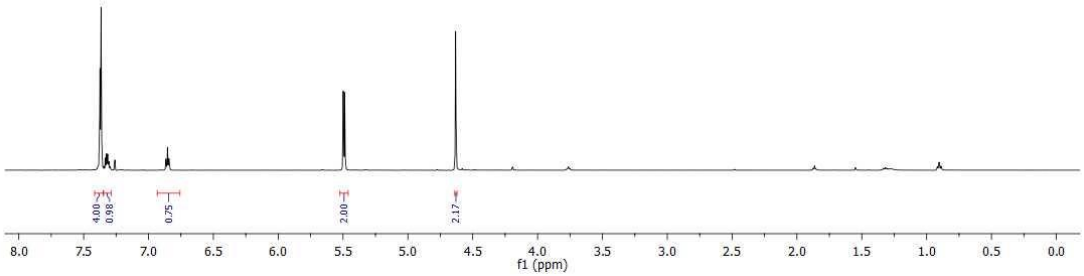
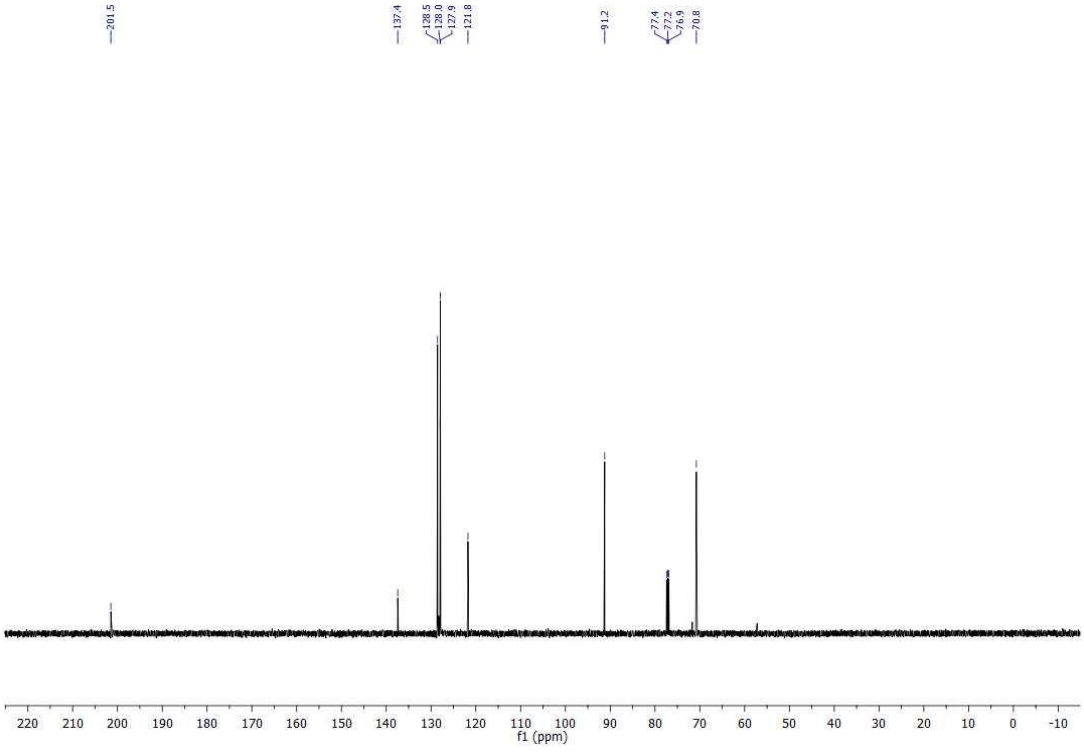
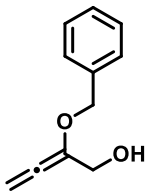
2.00
0.85
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

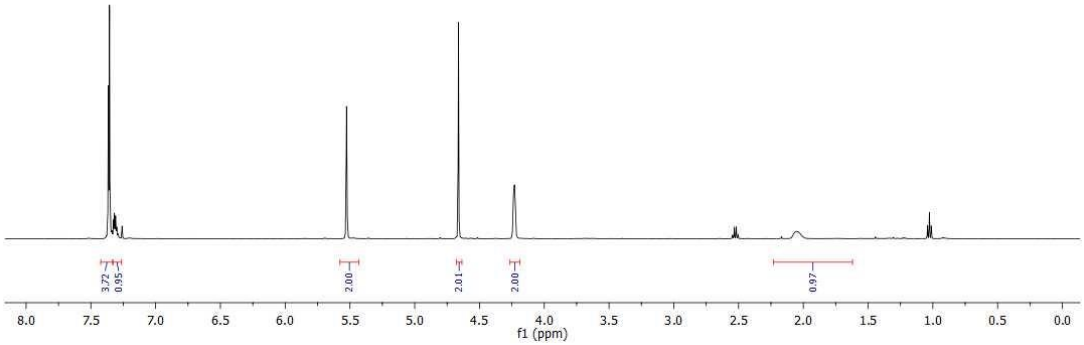

137.4
128.6
128.2
128.0
79.8
77.4
77.2
76.9
74.7
71.7
57.2
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

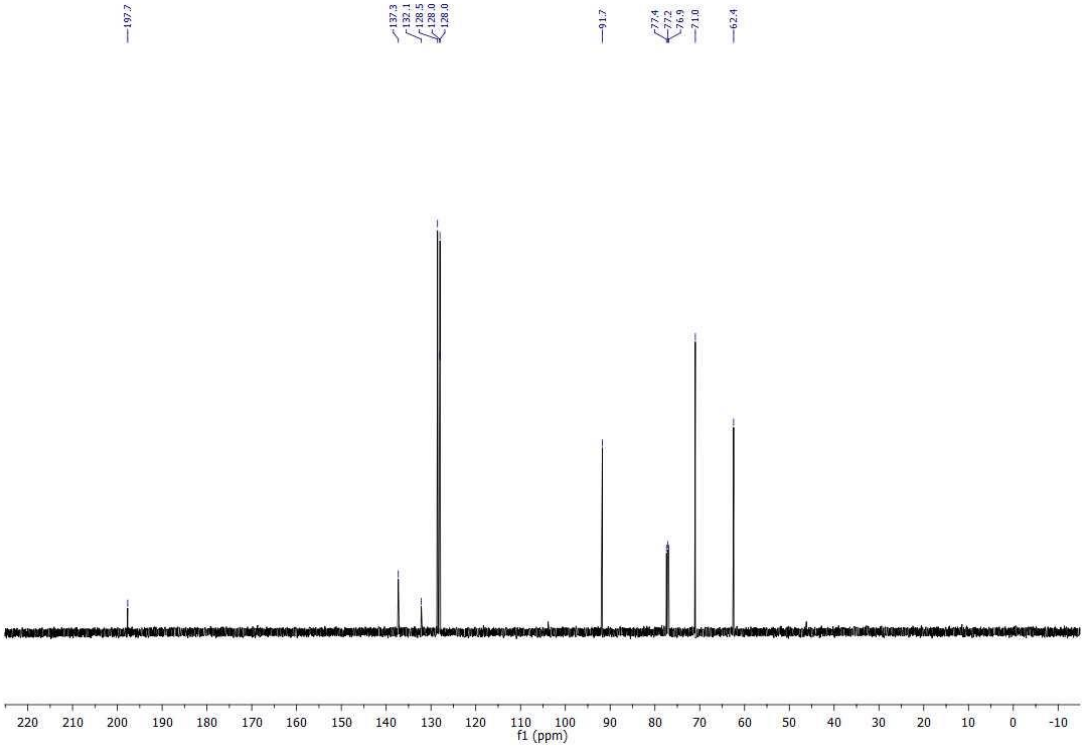


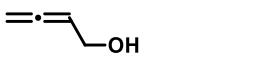

4.00
0.98
0.75
2.00
2.17
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

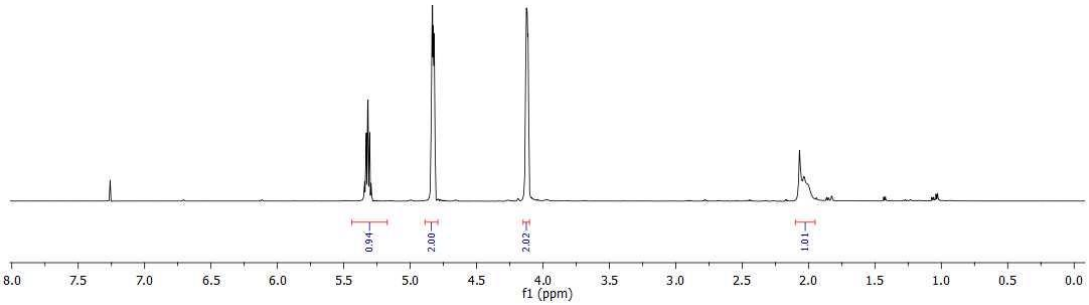

201.5
137.4
128.5
128.0
127.9
121.8
91.2
77.4
77.2
76.9
70.8
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

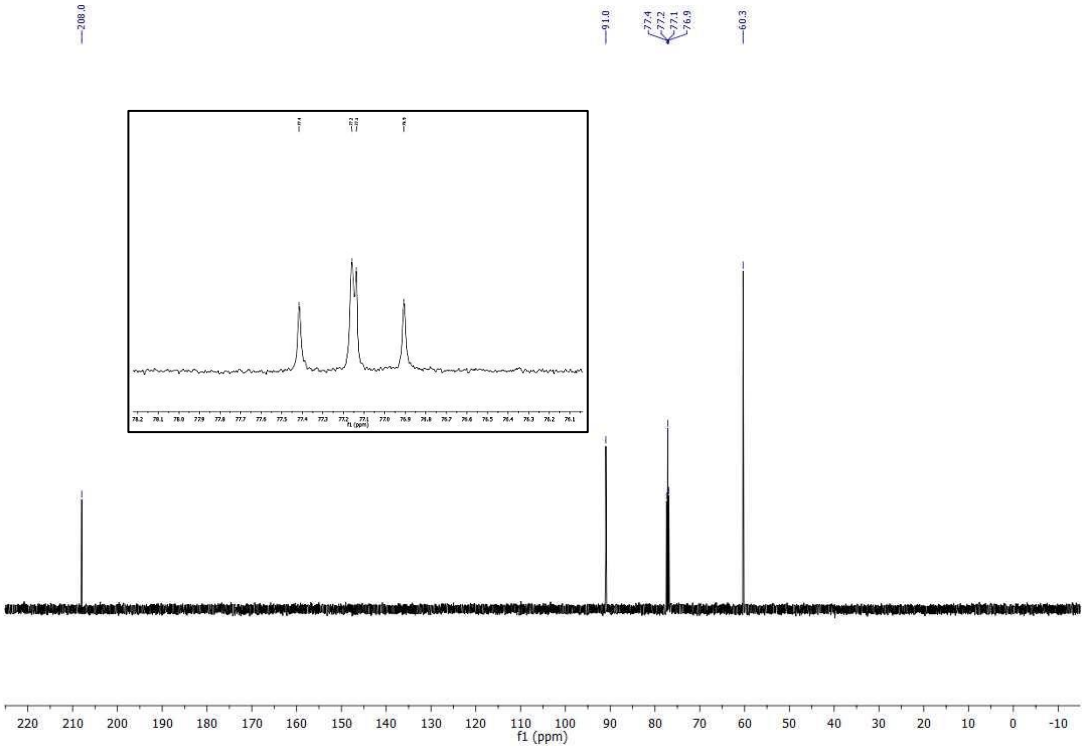

O
OH

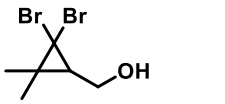

3.72
0.95
2.00
2.01
2.00
0.97
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

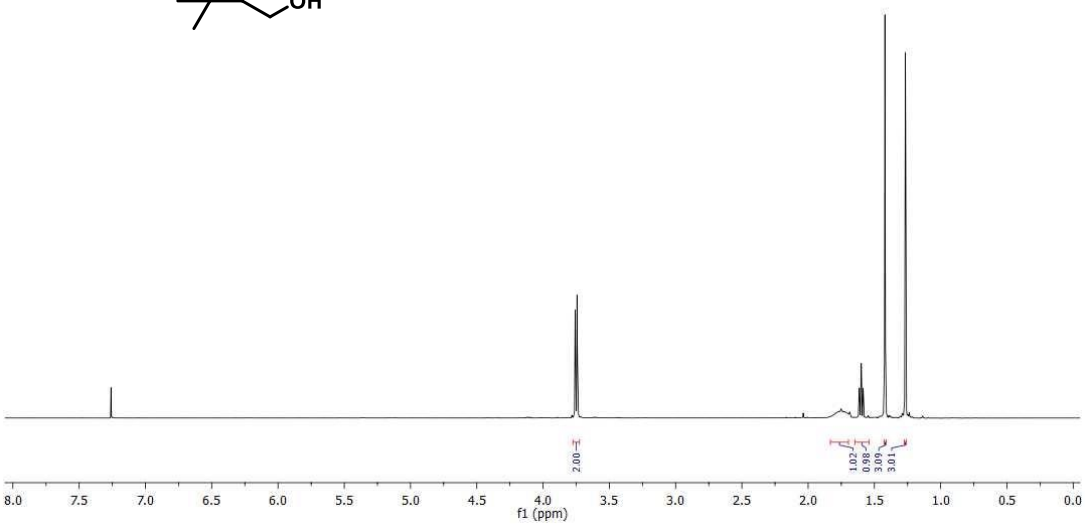

197.7
137.3
132.1
128.5
128.0
128.0
91.7
77.4
77.2
76.9
71.0
62.4
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH

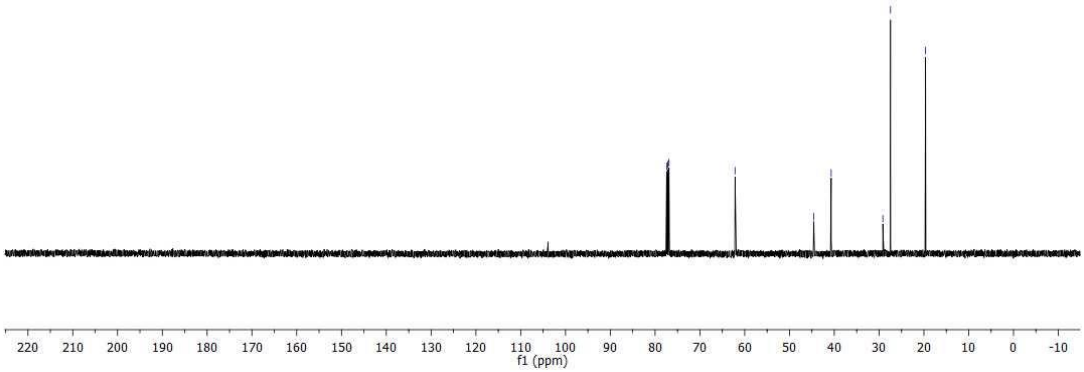

0.94
2.00
2.02
1.01
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

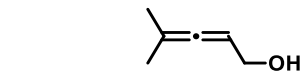

208.0
91.0
77.4
77.2
77.1
76.9
60.3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

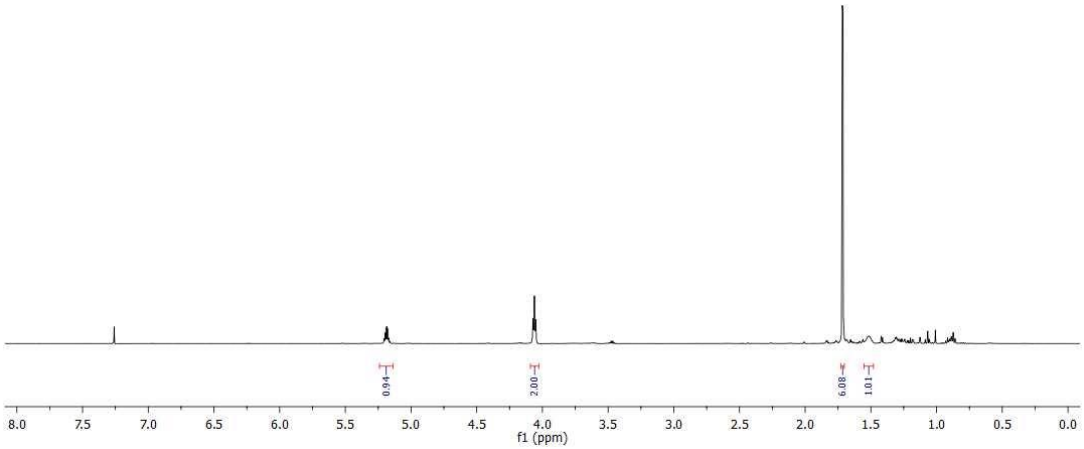

Br
Br
OH

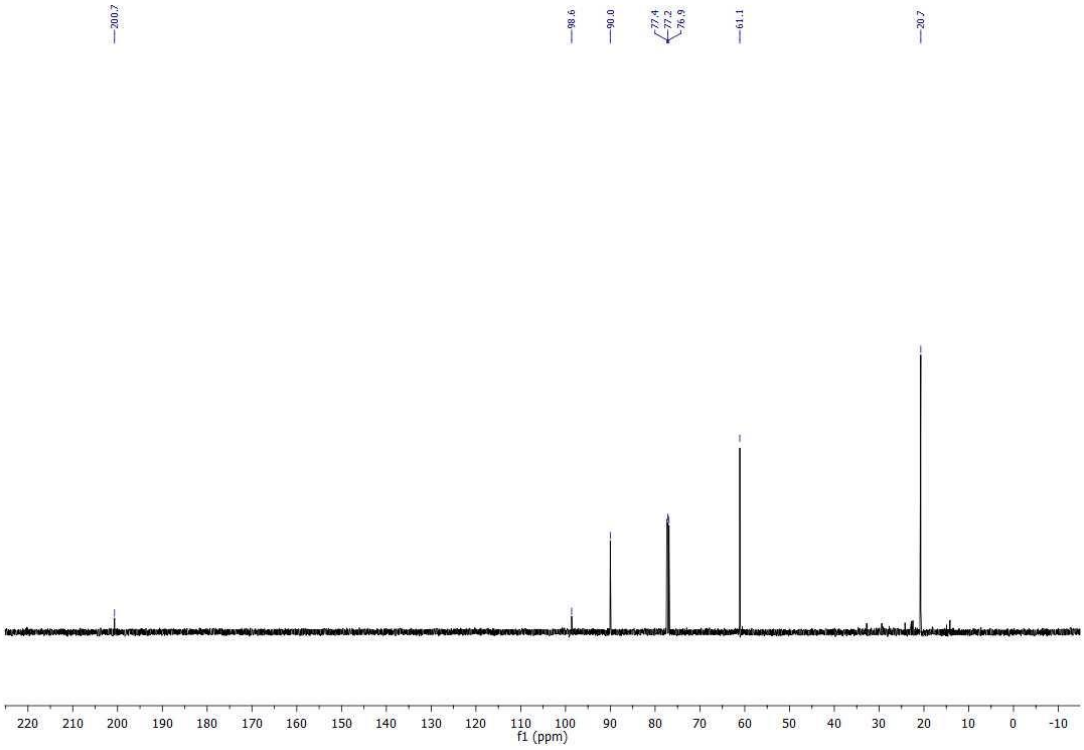

2.00
1.02
0.98
3.09
3.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

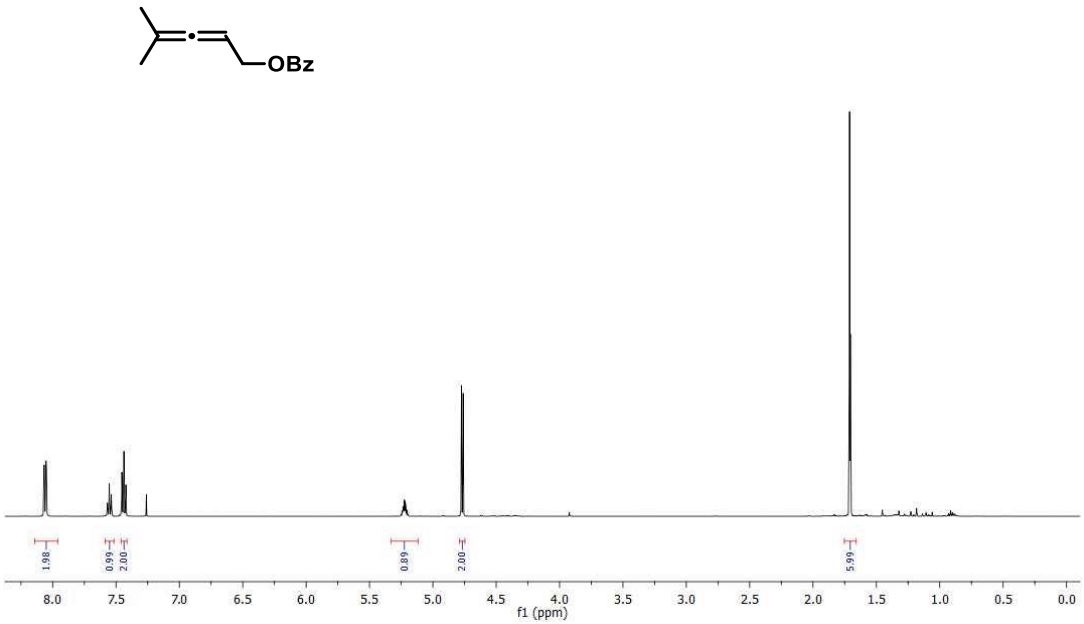

77.4
77.2
76.9
62.2
44.6
40.7
29.2
27.5
19.6

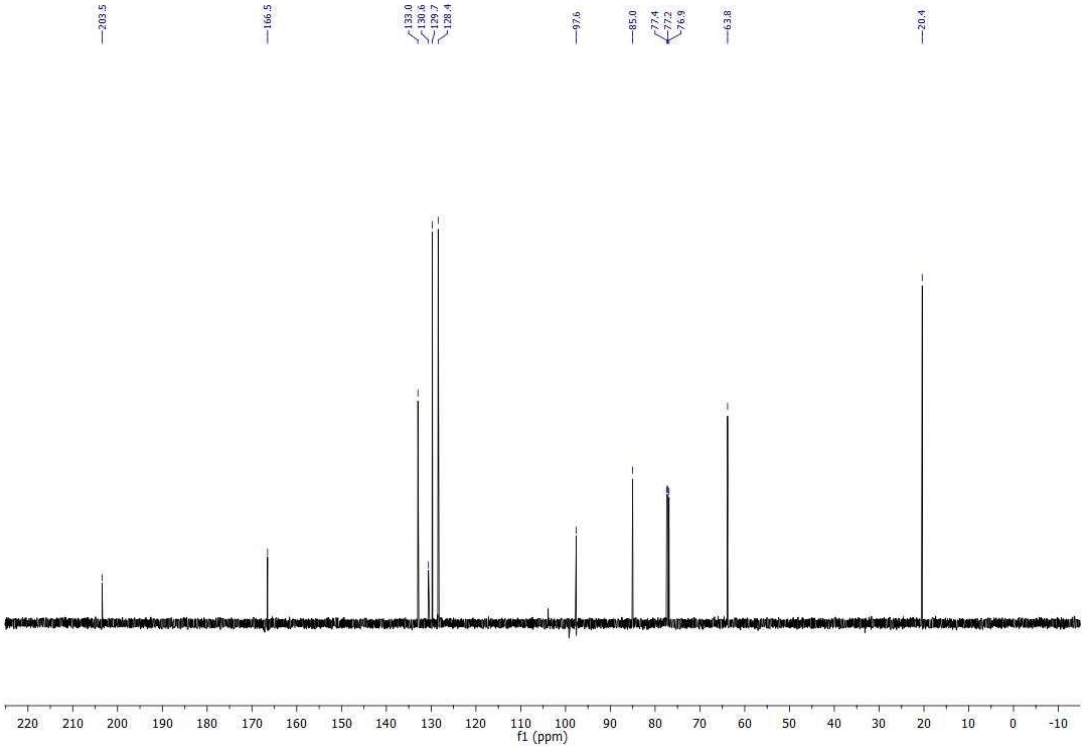

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

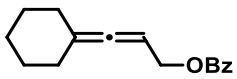

OH

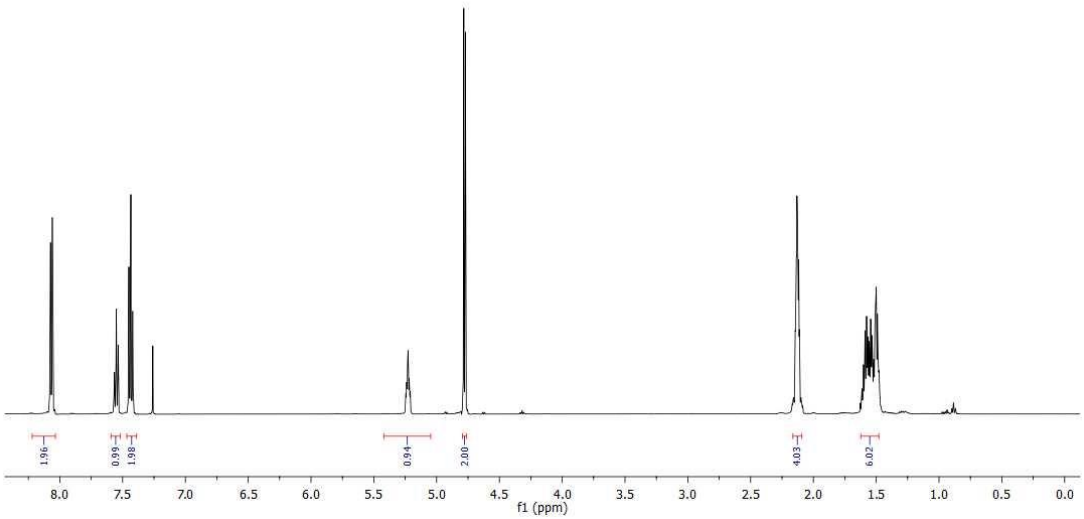

0.94
2.00
6.08
1.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

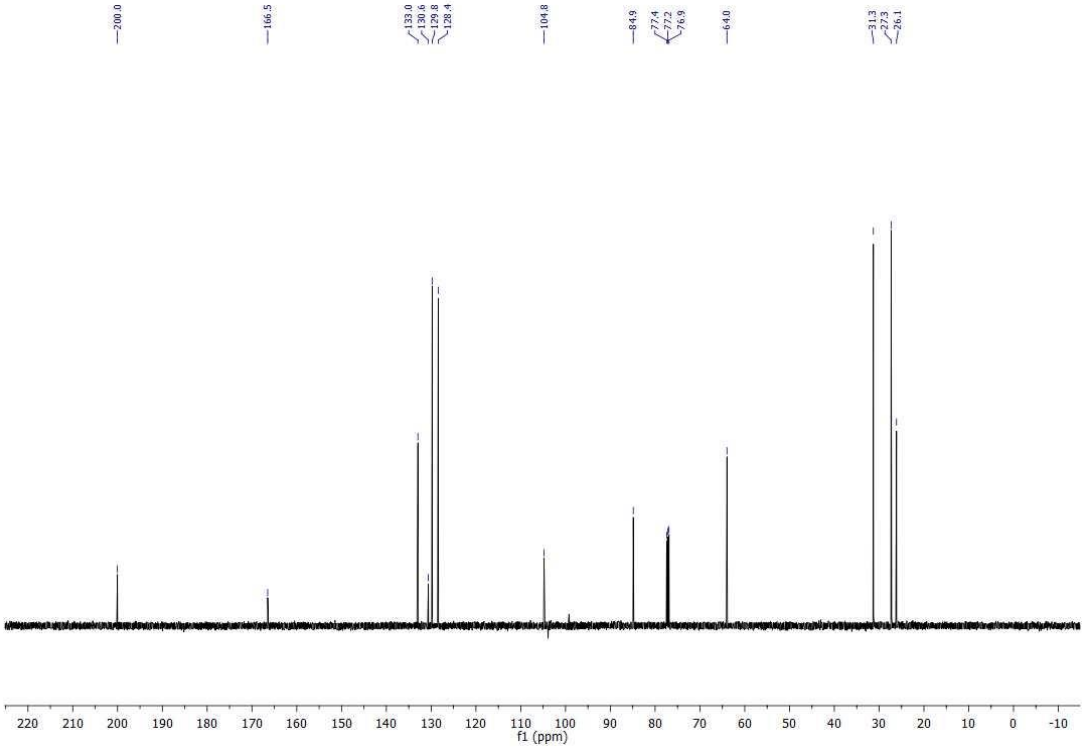

200.7
98.6
90.0
77.4
77.2
76.9
61.1
20.7
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

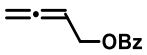

OBz
1.98
0.99
2.00
0.89
2.00
5.99
f1 (ppm)

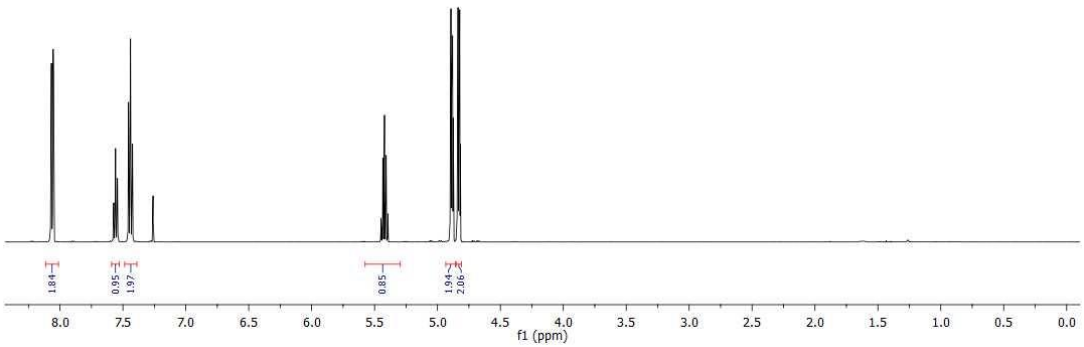

203.5
166.5
133.0
130.6
129.7
128.4
97.6
85.0
77.4
77.2
76.9
63.8
20.4
f1 (ppm)


OBz


1.96
0.99
1.98
0.94
2.00
4.03
6.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200.0
166.5
133.0
130.6
129.8
128.4
104.8
84.9
77.4
77.2
76.9
64.0
31.3
27.3
26.1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OBz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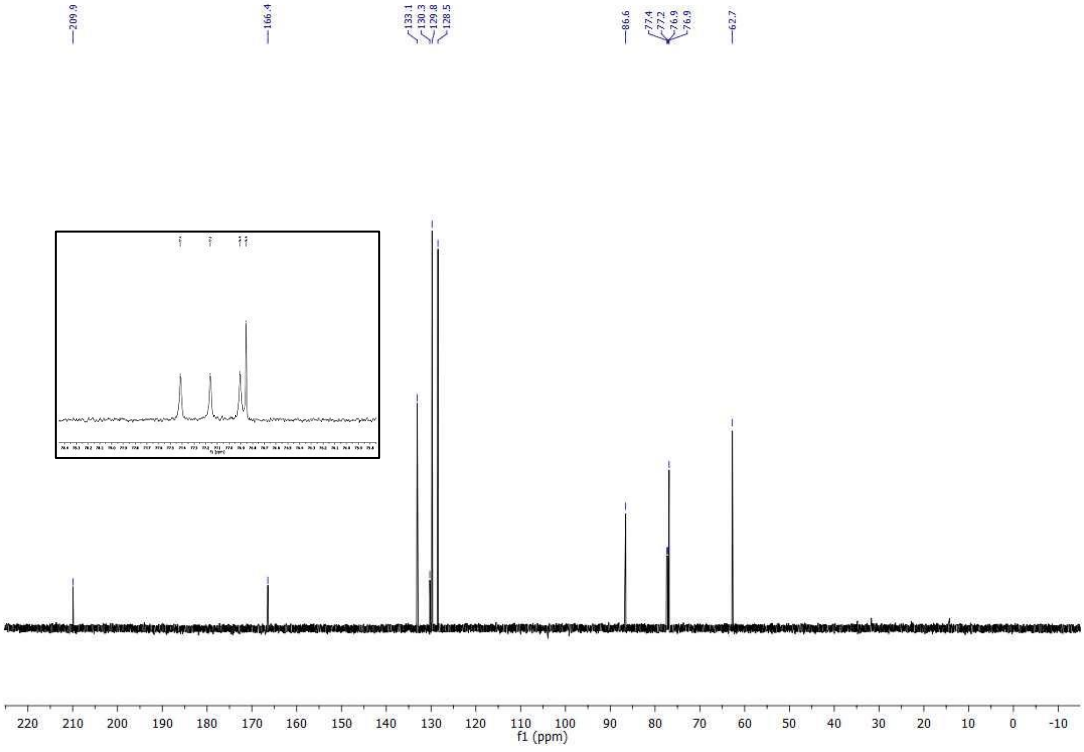
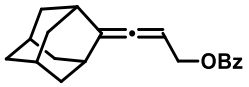
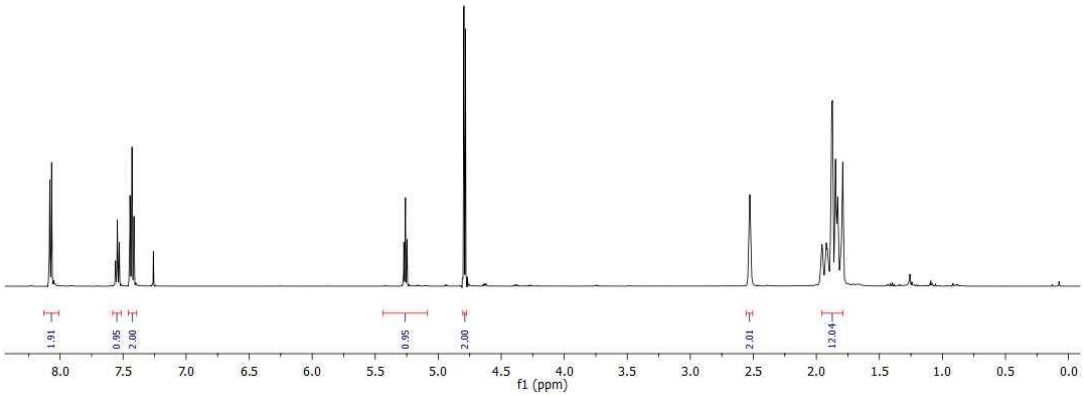
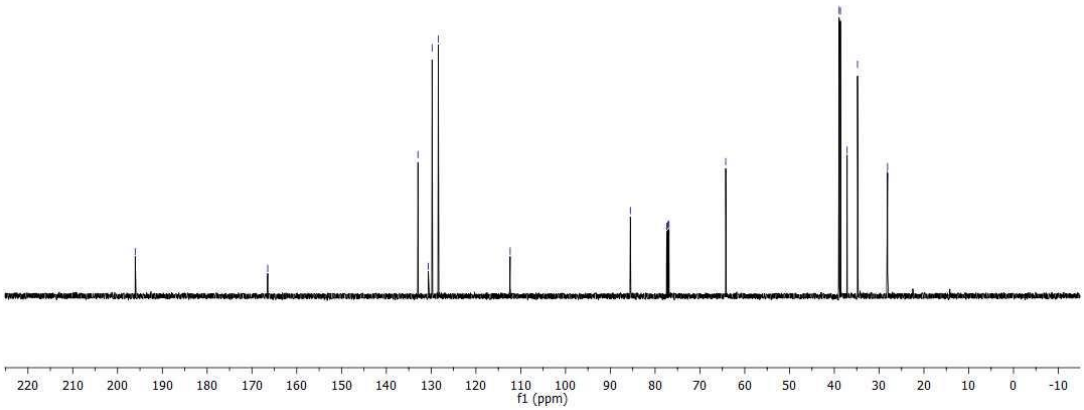
0.95
1.97
0.85
1.94
2.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

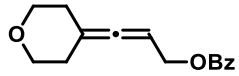

209.9
166.4
133.1
130.3
129.8
128.5
86.6
77.4
77.2
76.9
76.9
62.7
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OBz

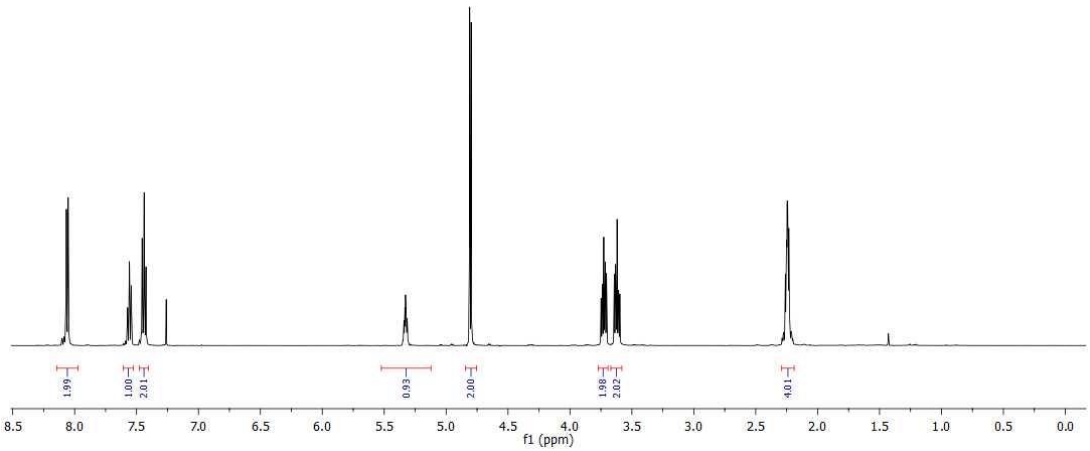

1.91
0.95
2.00
0.95
2.00
2.01
12.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

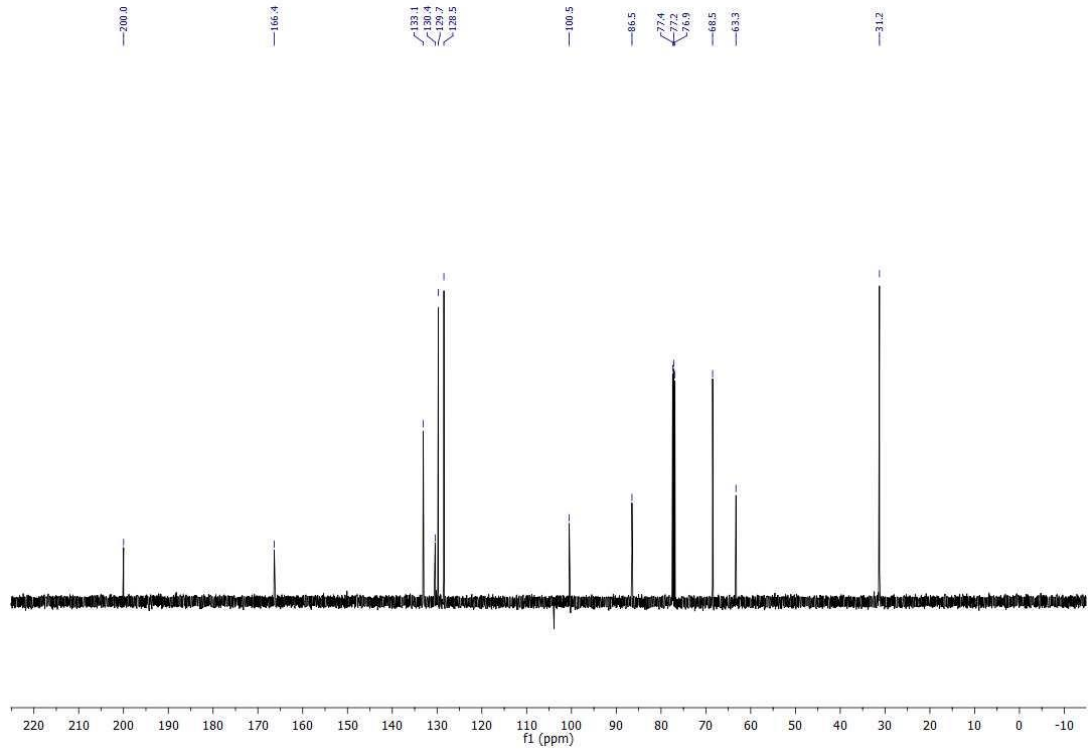

196.1
166.5
132.9
130.6
130.3
128.4
112.4
85.5
77.4
77.2
76.9
64.2
38.9
38.6
37.1
34.8
28.1
28.1

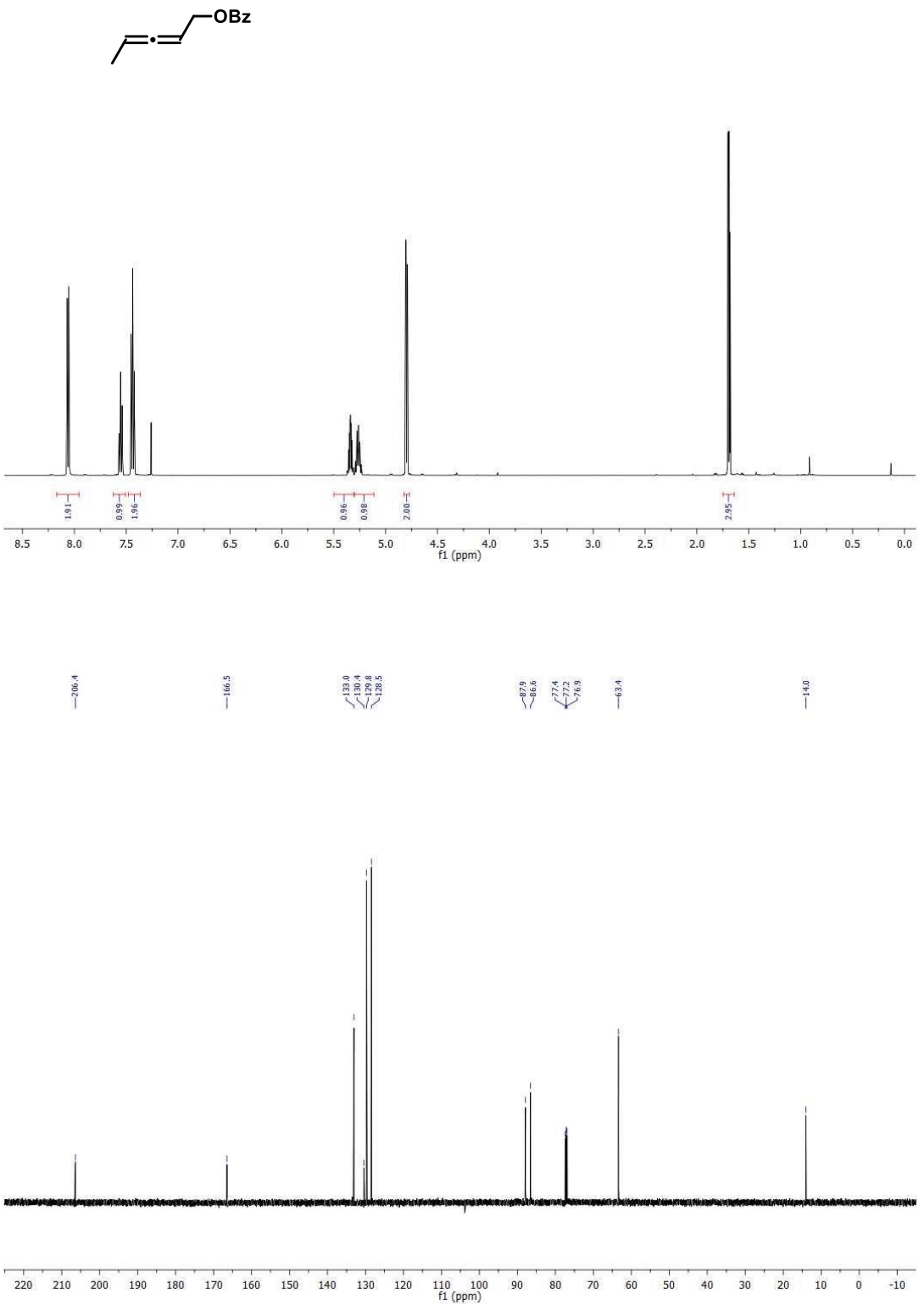

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

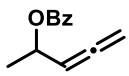

O
OBz

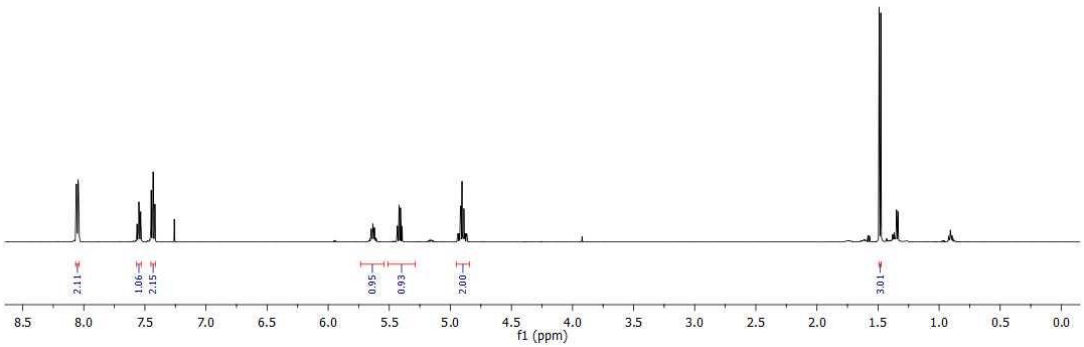
33


1.99
1.00
2.01
0.93
2.00
1.98
2.02
4.01
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

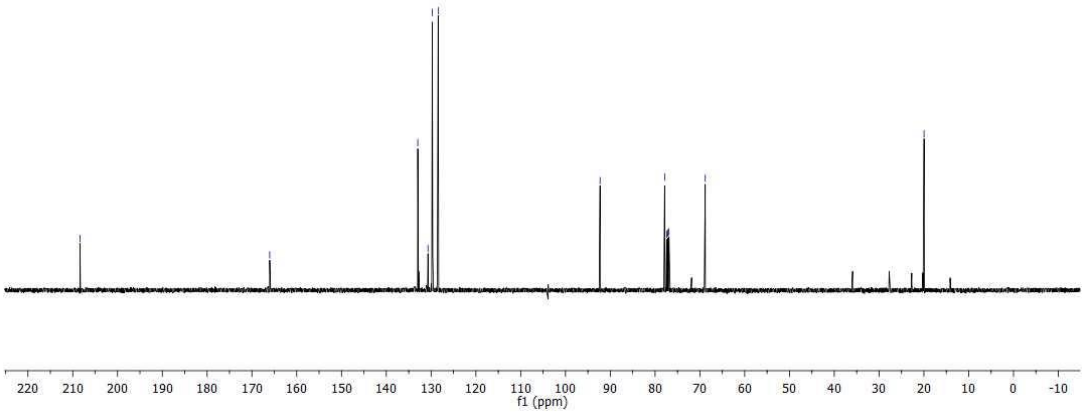

200.0
166.4
133.1
130.4
130.2
129.7
128.5
100.5
86.5
77.4
77.2
76.9
68.5
63.3
31.2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

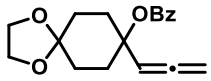

OBz
1.91
0.99
1.96
0.96
0.98
2.00
2.95
f1 (ppm)
206.4
166.5
133.0
130.4
129.8
128.5
87.9
86.6
77.4
77.2
76.9
63.4
14.0
f1 (ppm)

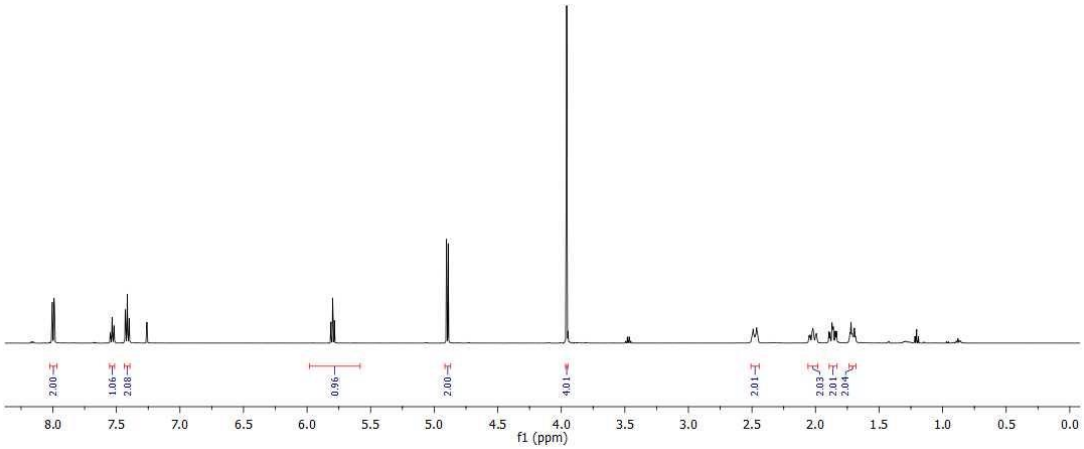

OBz


2.11
1.06
2.15
0.95
0.93
2.00
3.01
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

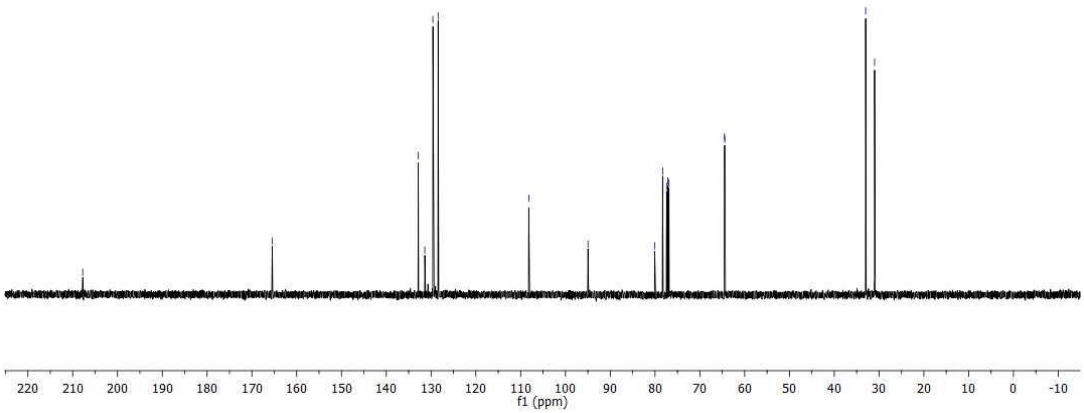

208.4
166.0
133.0
130.7
129.7
128.4
92.3
77.9
77.4
77.2
76.9
68.8
20.0

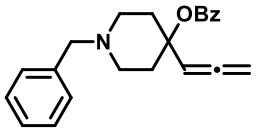

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

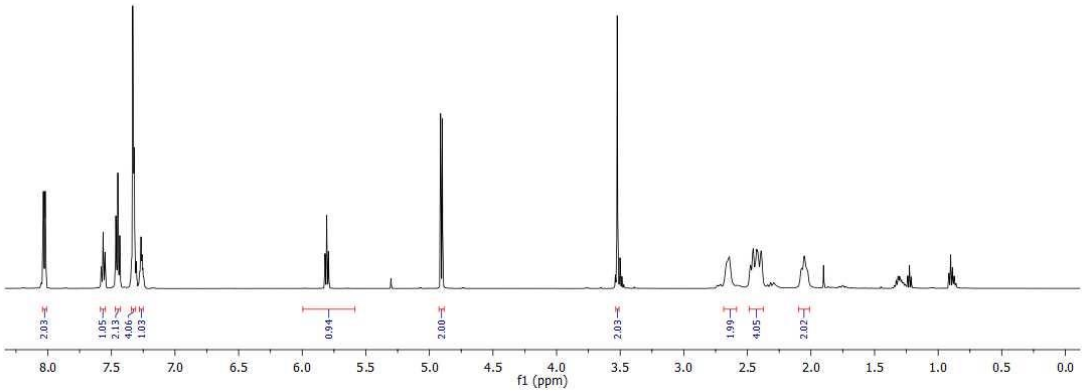

OBz
O
O


2.00
1.06
2.08
0.96
2.00
4.01
2.01
2.03
2.01
2.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

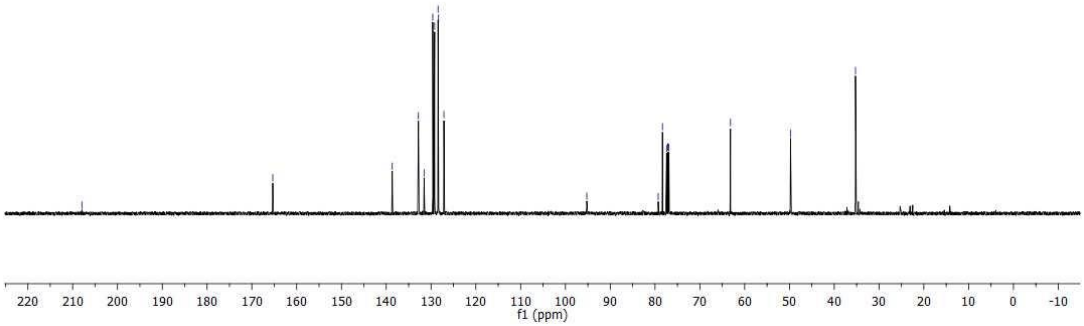

207.7
165.5
132.9
131.4
129.6
128.4
108.2
95.0
80.1
78.3
77.4
77.2
76.9
64.5
64.4
33.0
31.0


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OBz
N


2.03
1.05
2.13
4.06
1.03
0.94
2.00
2.03
1.99
4.05
2.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


207.9
165.3
138.7
132.8
131.6
129.6
129.2
128.4
128.3
127.1
95.2
79.3
78.3
77.4
77.2
76.9
63.2
49.7
35.3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200
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180
170
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140
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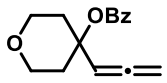
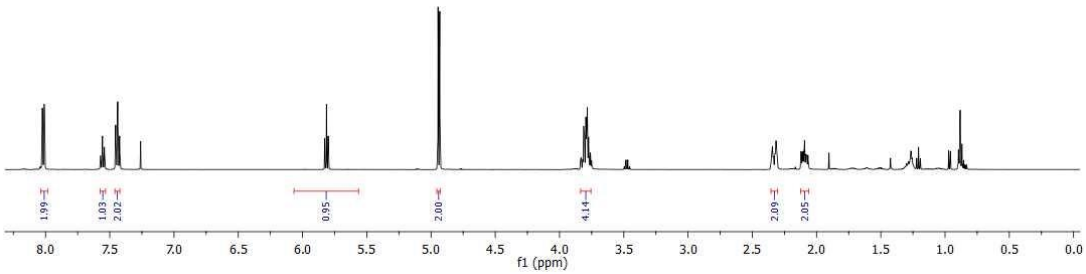
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OBz
O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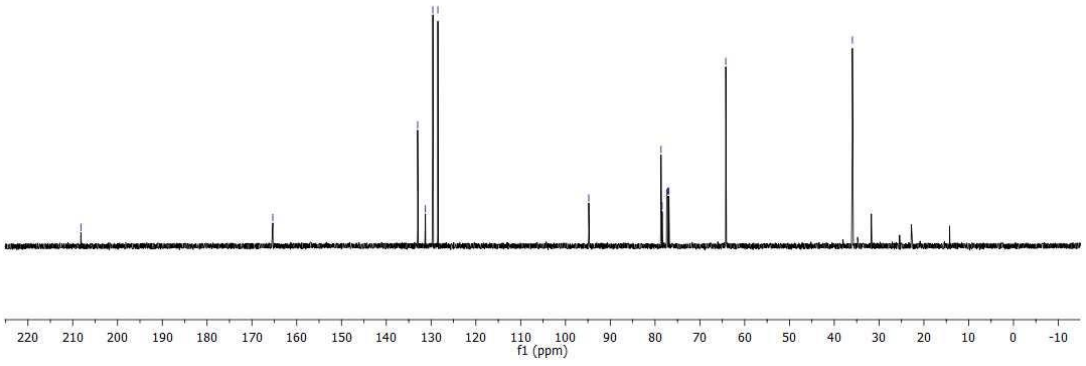
1.03
2.02
0.95
2.00
4.14
2.09
2.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


208.2
165.3
133.0
131.3
129.6
128.5
94.8
78.7
78.4
77.4
77.2
76.9
64.2
36.0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210
200
190
180
170
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140
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120
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100
90
80
70
60
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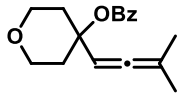
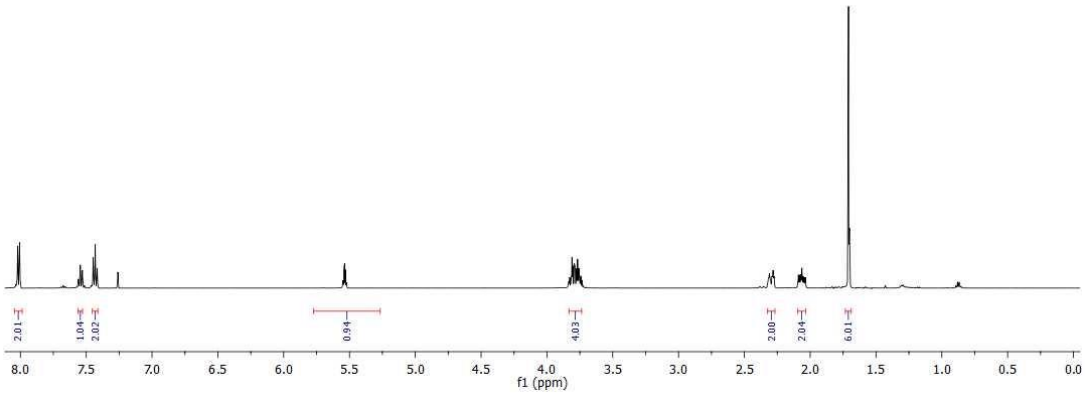
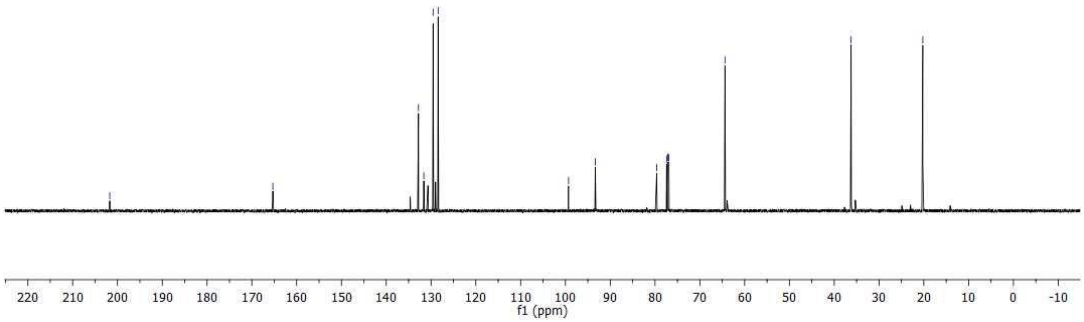
40
30
20
10
0
-10
f1 (ppm)


OBz
O


2.01
1.04
2.02
0.94
4.03
2.00
2.04
6.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


201.7
165.3
132.8
131.6
129.5
128.4
99.3
93.3
79.6
77.4
77.2
76.9
64.4
36.2
20.2


220
210
200
190
180
170
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140
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120
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100
90
80
70
60
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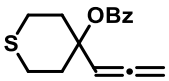
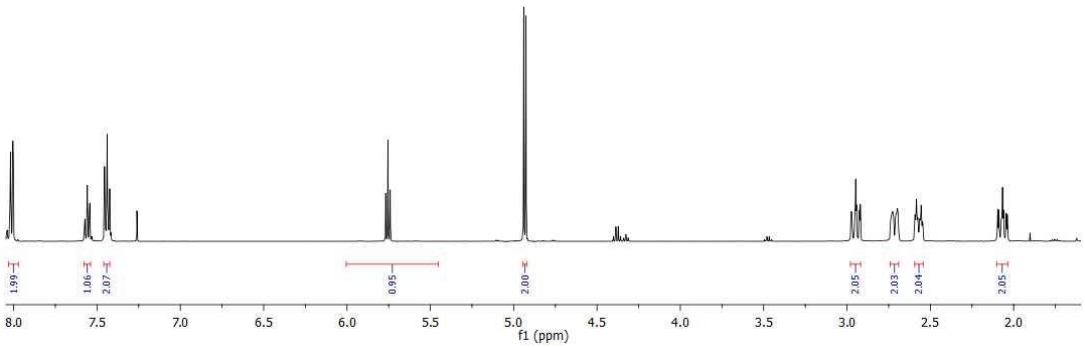
40
30
20
10
0
-10
f1 (ppm)


OBz
S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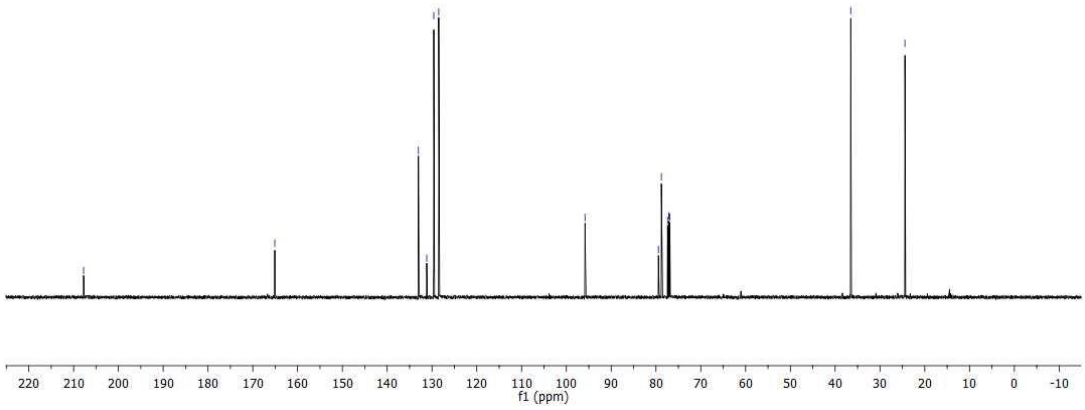
1.06
2.07
0.95
2.00
2.05
2.03
2.04
2.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)


207.8
165.1
133.0
131.2
129.6
128.5
95.8
79.5
78.8
77.4
77.2
76.9
36.5
24.4


220
210
200
190
180
170
160
150
140
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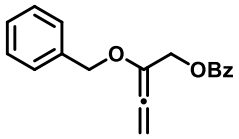
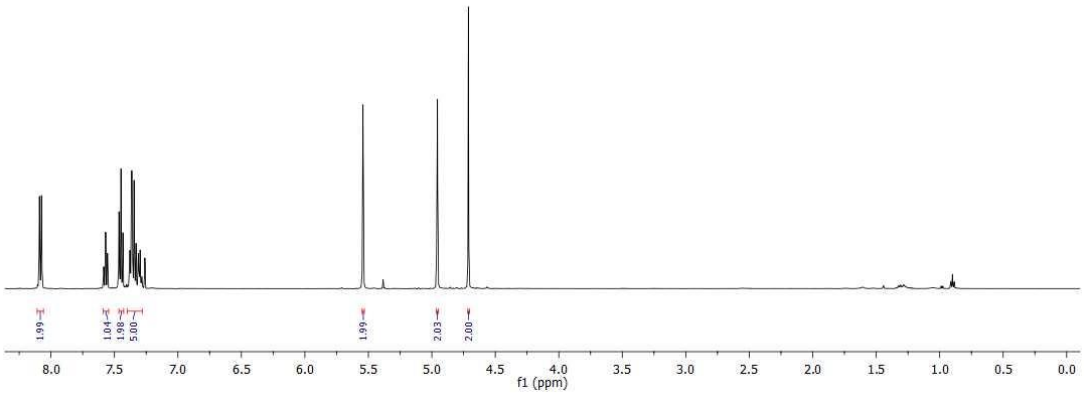
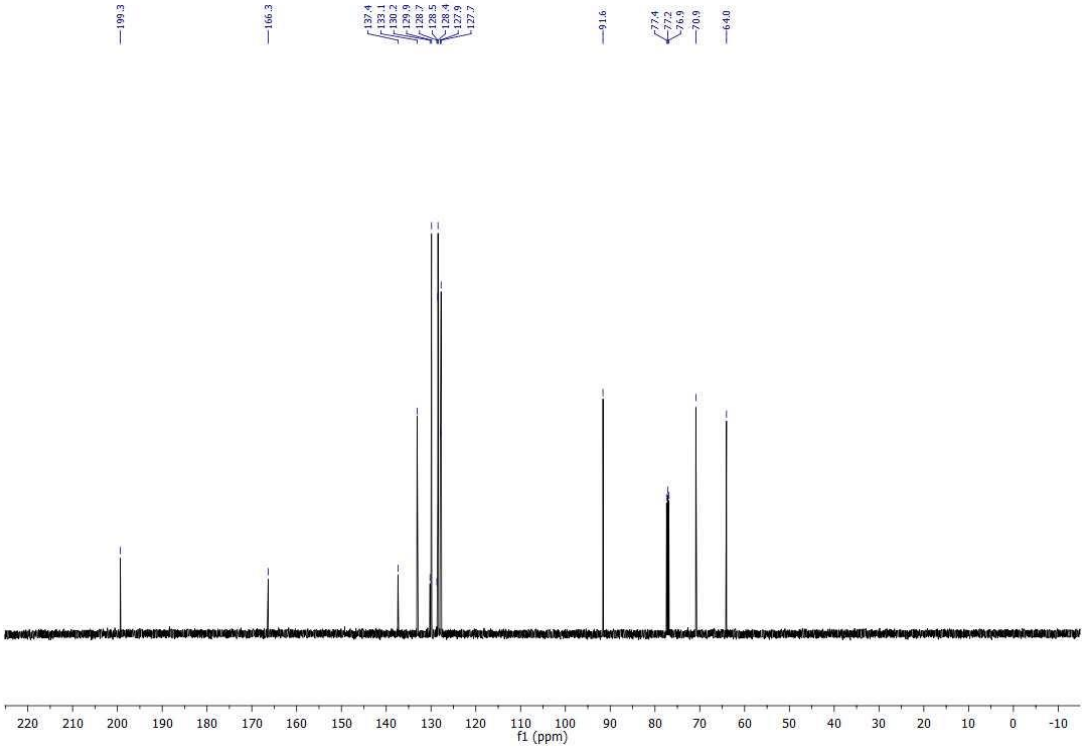
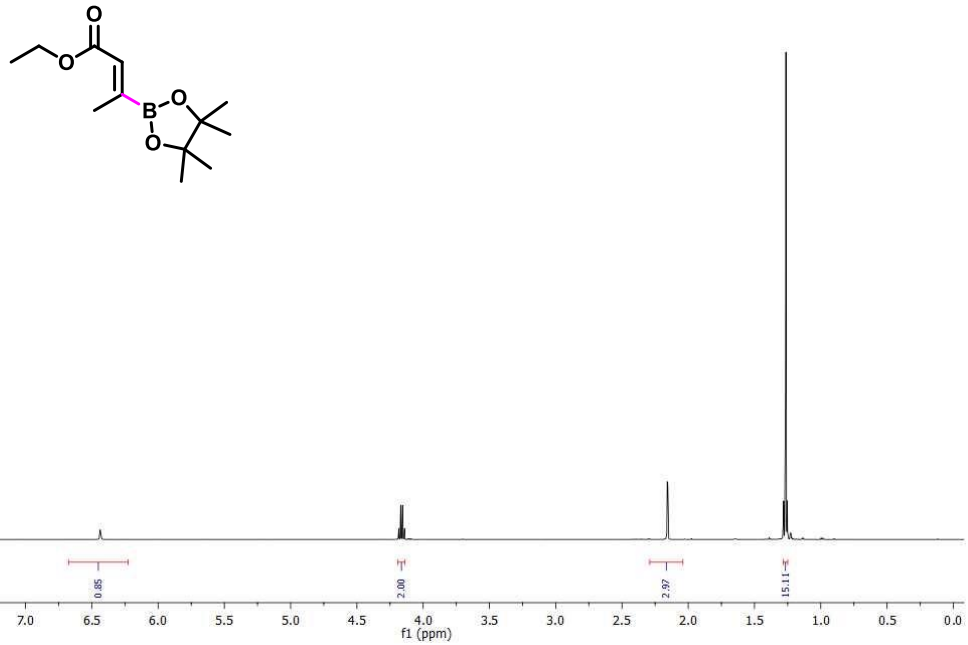
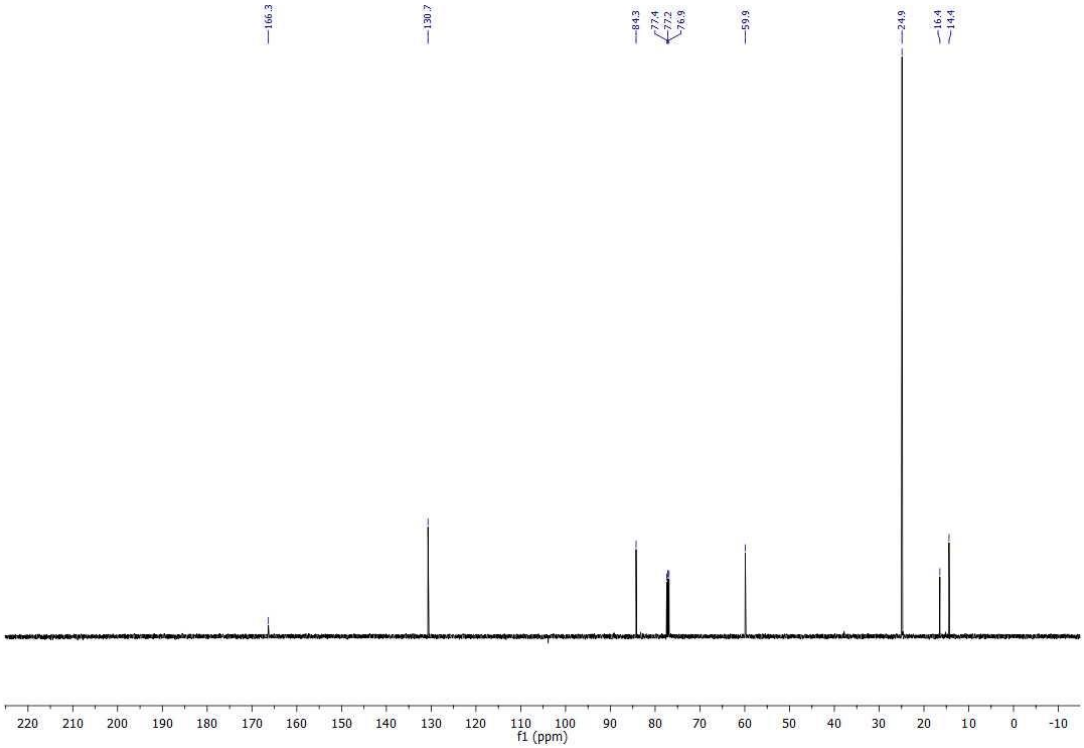
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

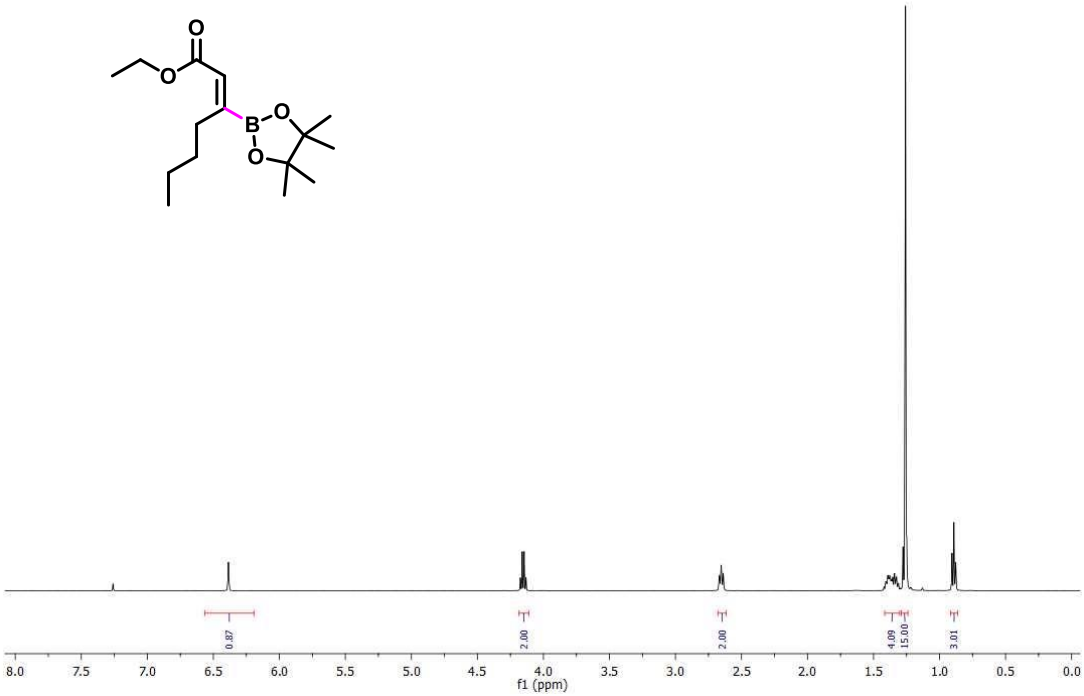

O
OBz

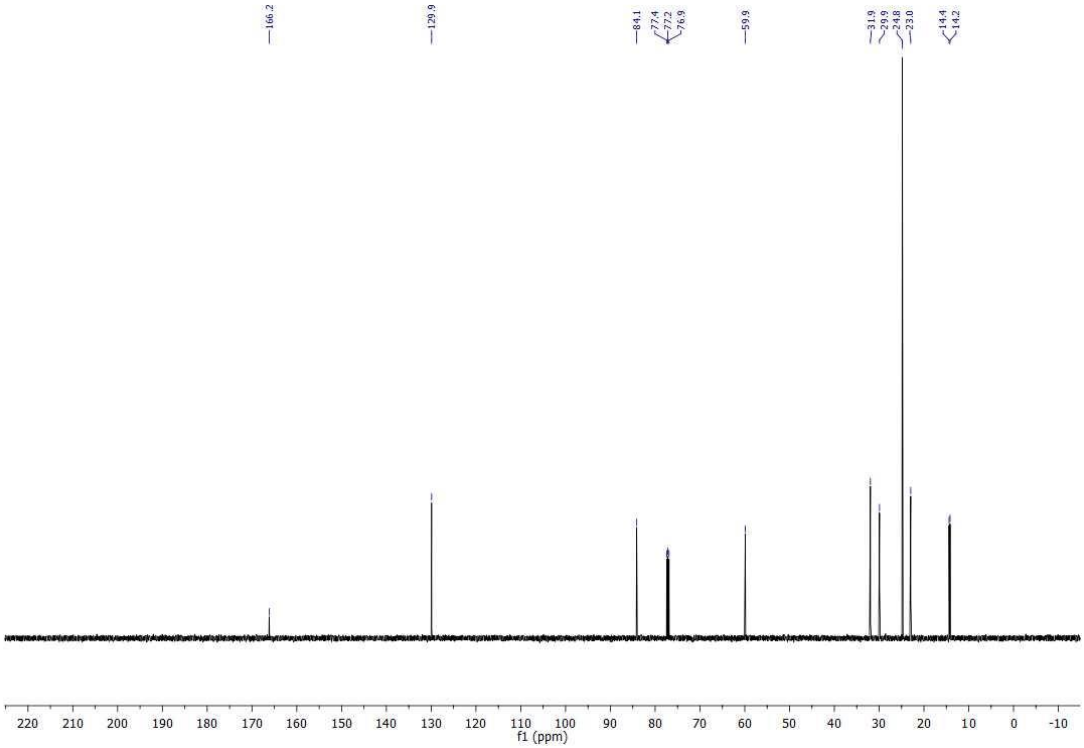

1.99
1.04
1.98
5.00
1.99
2.03
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

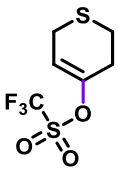

199.3
166.3
137.4
133.1
130.2
129.9
128.7
128.5
128.4
127.9
127.7
91.6
77.4
77.2
76.9
70.9
64.0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

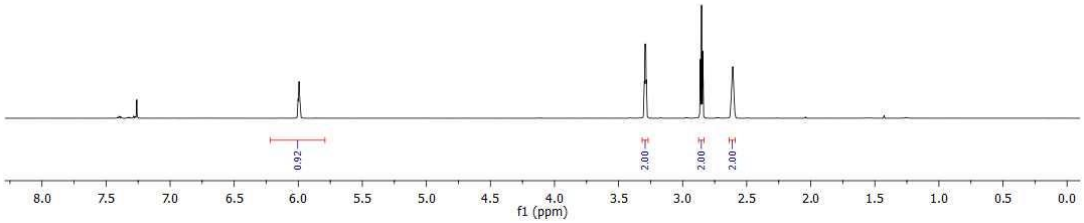

O
O
B
O
O
0.85
2.00
2.97
15.11
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

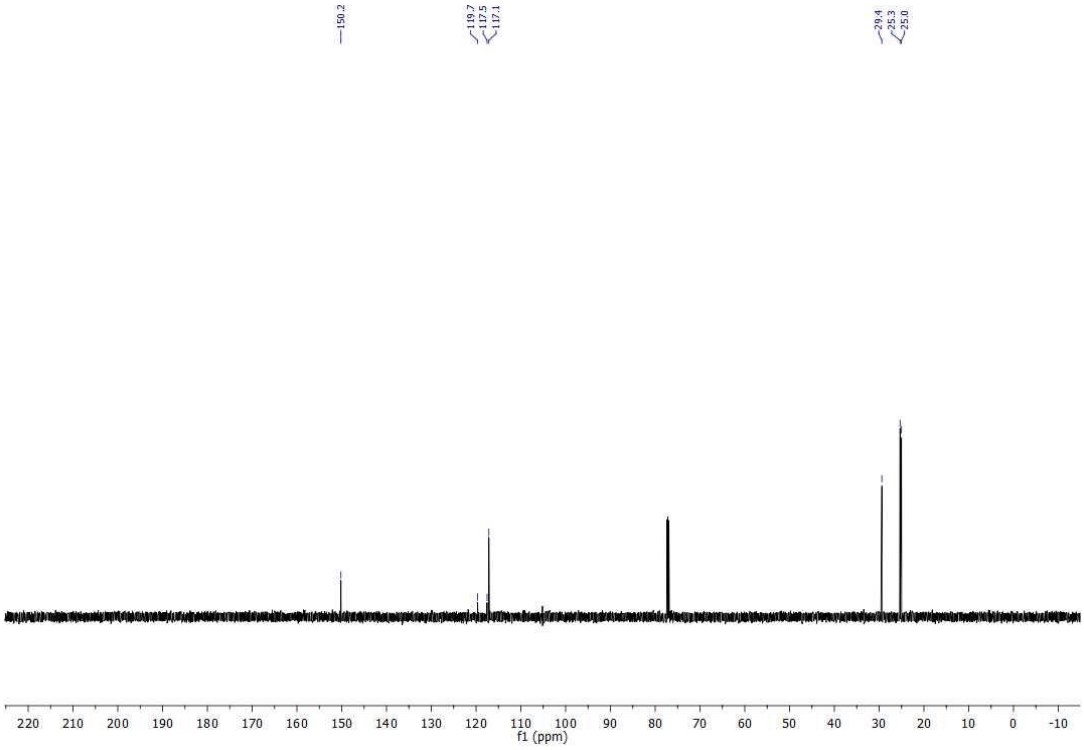

166.3
130.7
84.3
77.4
77.2
76.9
59.9
24.9
16.4
14.4
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

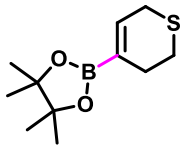

0.87
2.00
2.00
4.09
15.00
3.01
f1 (ppm)

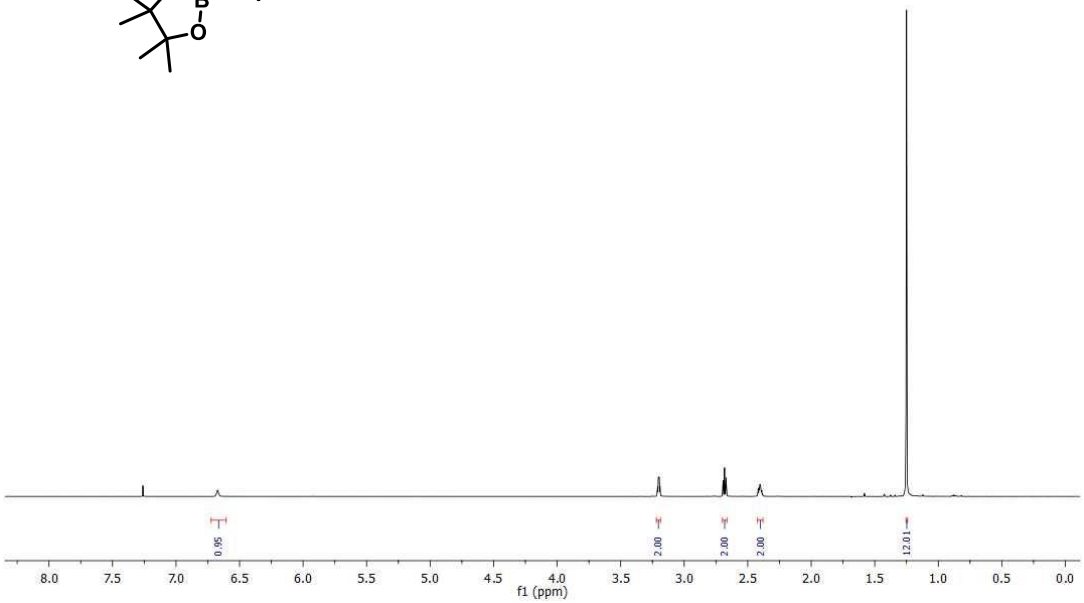

166.2
129.9
84.1
77.4
77.2
76.9
59.9
31.9
29.9
24.8
23.0
14.4
14.2
f1 (ppm)

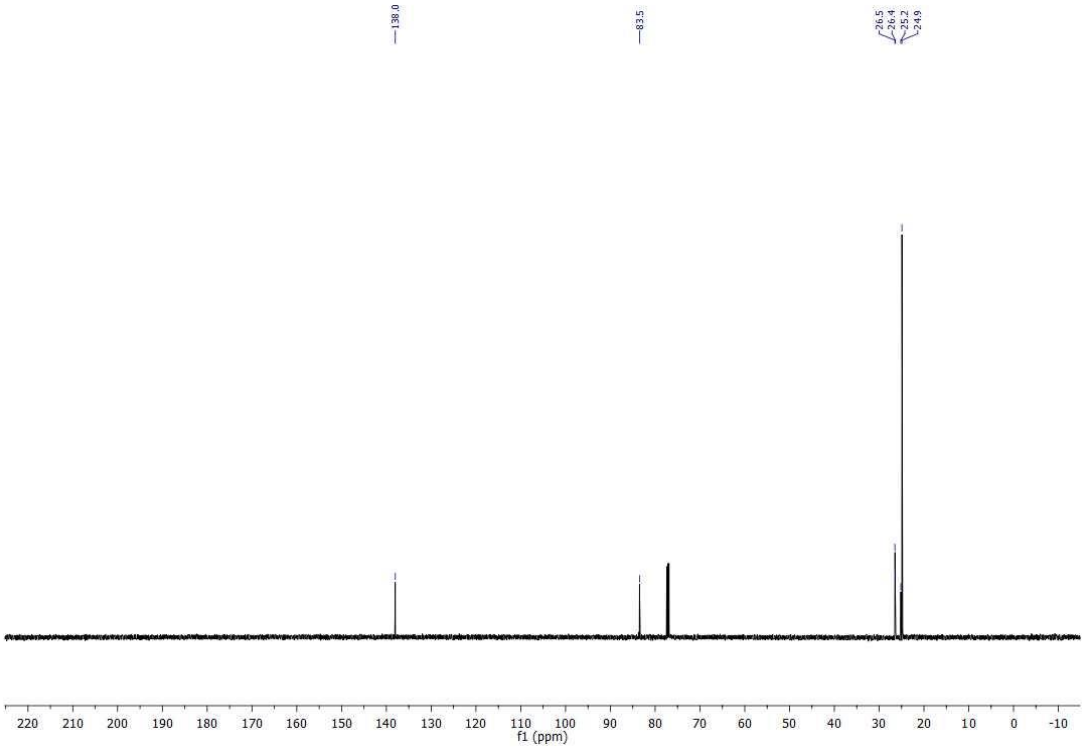

S
F3C
O
S
O
O

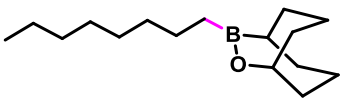

0.92
2.00
2.00
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

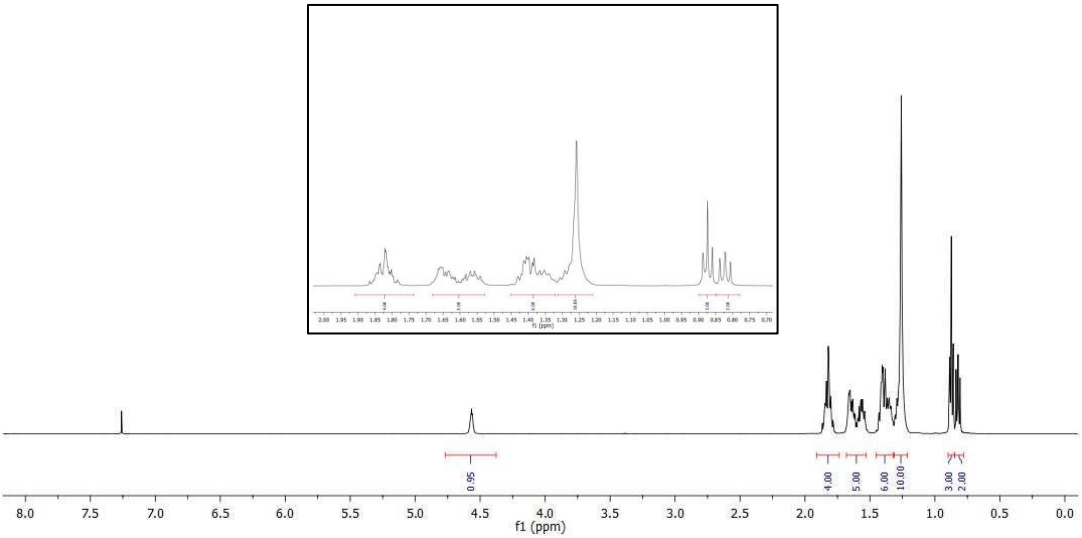

150.2
119.7
117.5
117.1
29.4
25.3
25.0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


S
O
B
O


0.95
2.00
2.00
2.00
12.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


138.0
83.5
26.5
26.4
25.2
24.9
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


B
O


0.95
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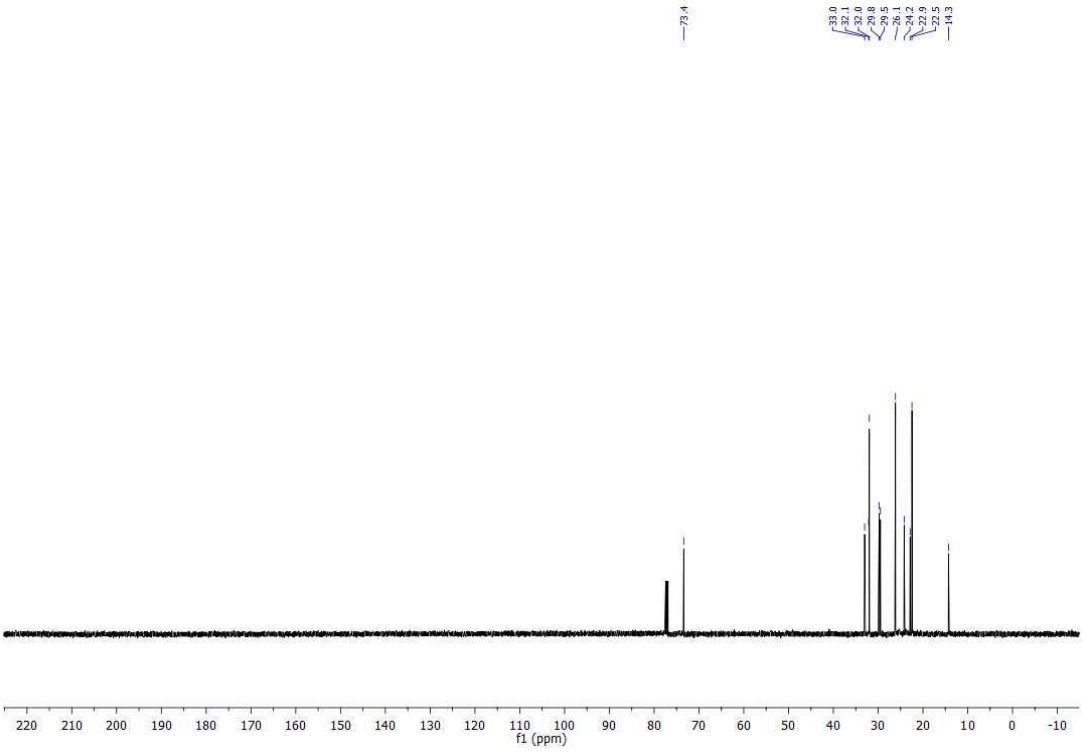
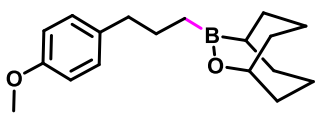
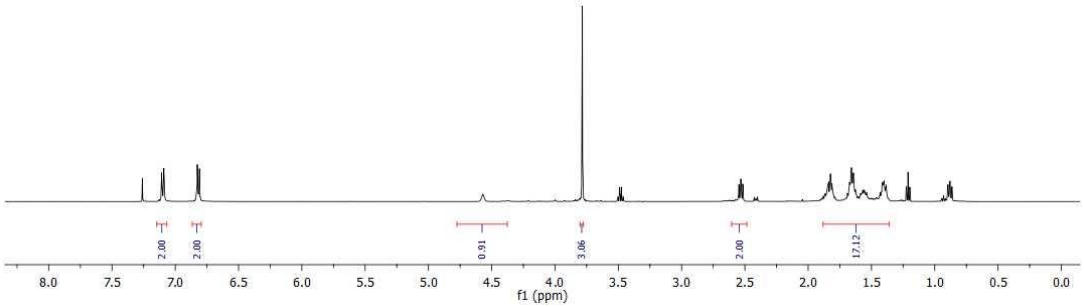
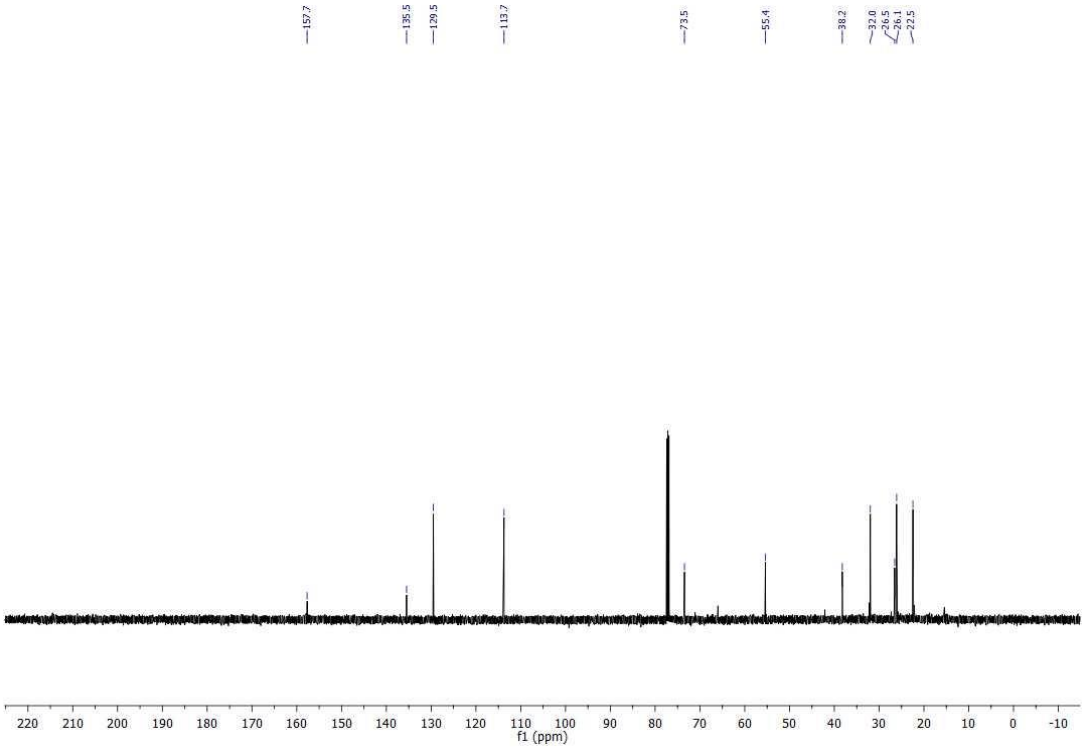
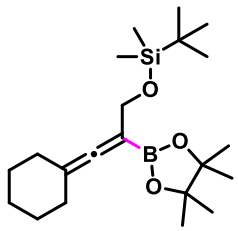
5.00
6.00
10.00
3.00
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

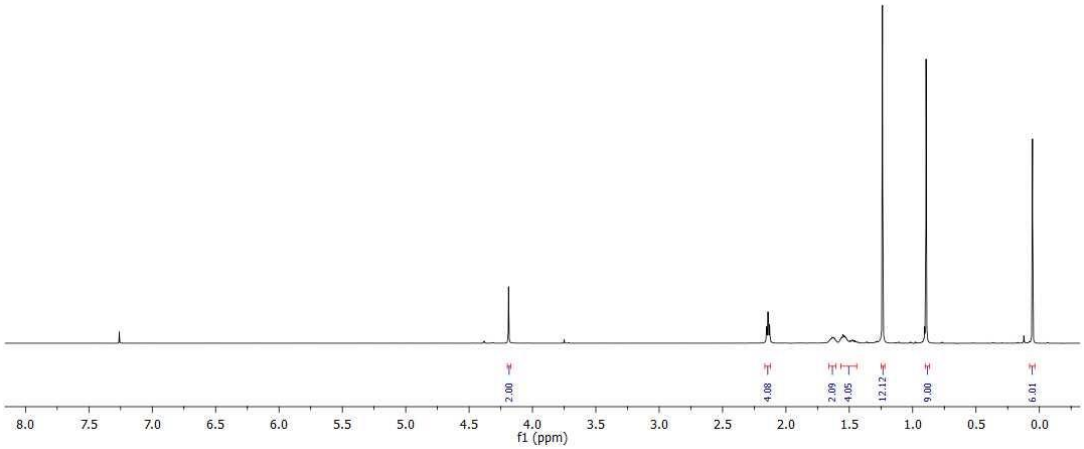

73.4
33.0
32.1
32.0
29.8
29.5
26.1
24.2
23.9
22.5
14.3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

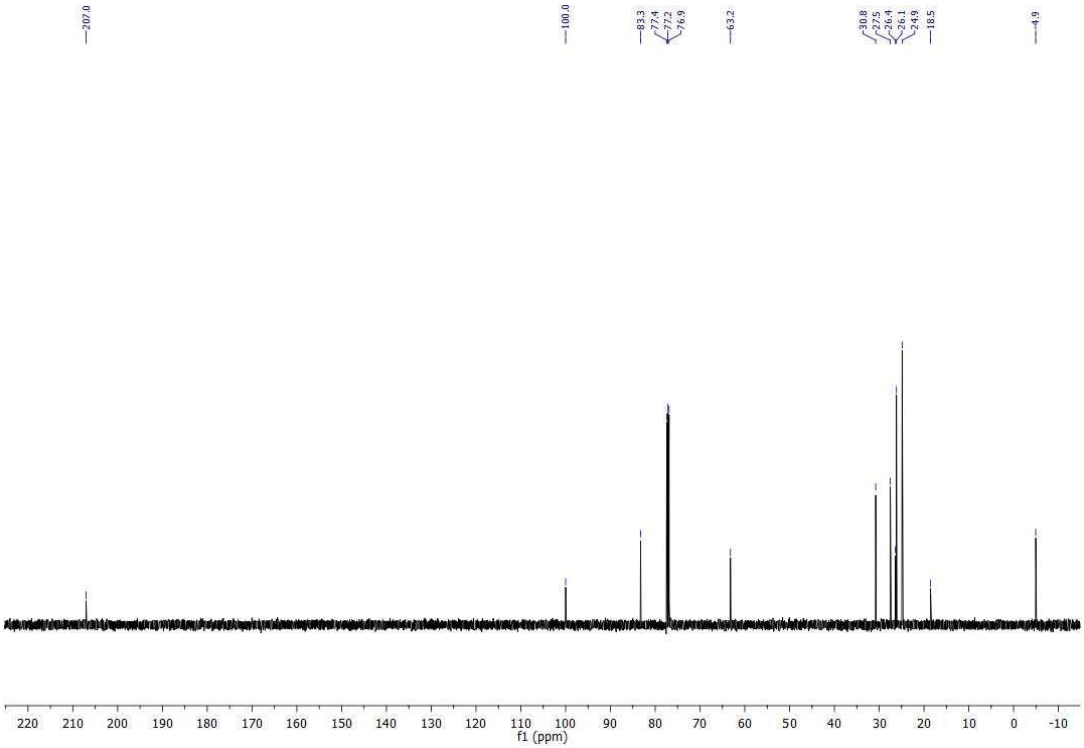

B
O
O

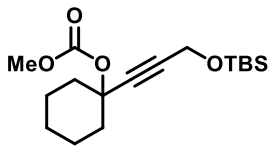

2.00
2.00
0.91
3.06
2.00
17.12
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

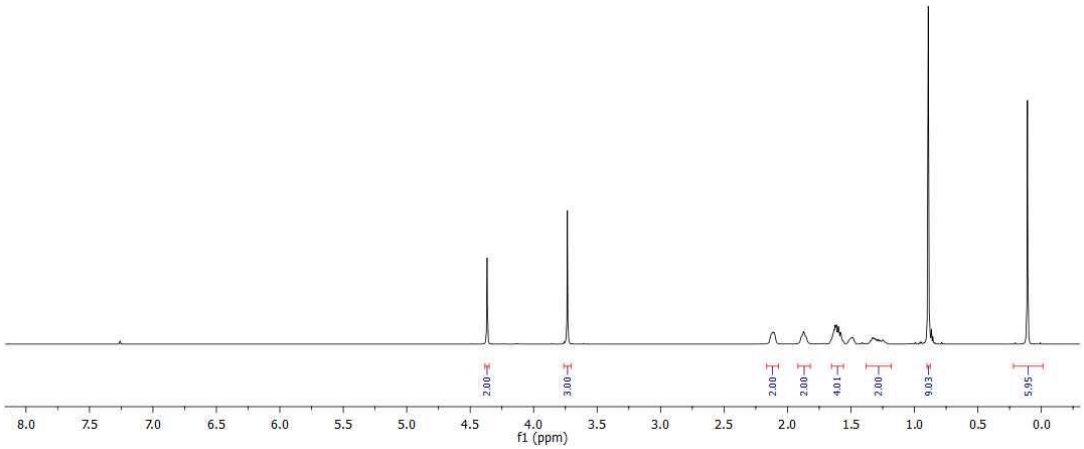

157.7
135.5
129.5
113.7
73.5
55.4
38.2
32.0
26.5
26.1
22.5
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

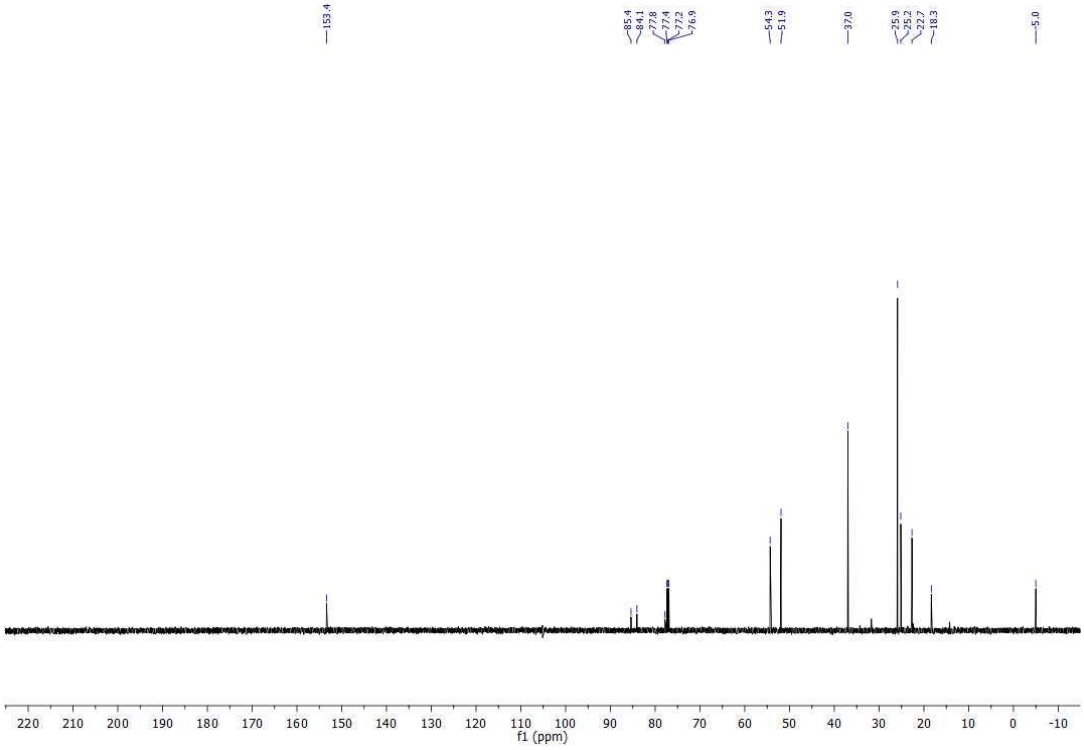

Si
O
B
O
O

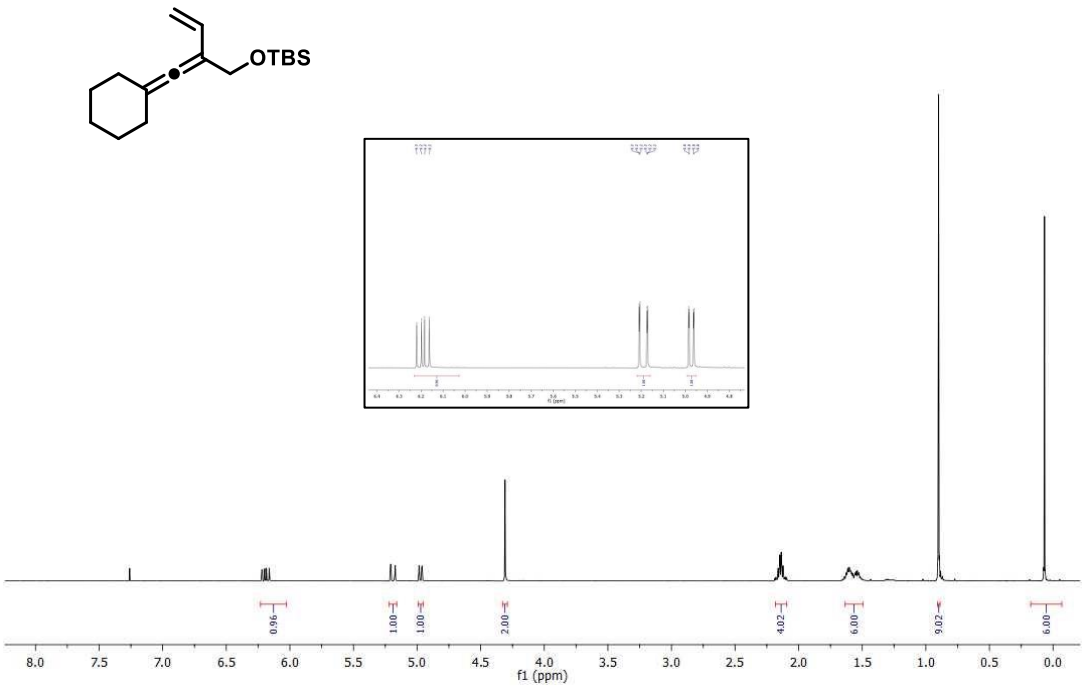

2.00
4.08
2.09
4.05
12.12
9.00
6.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

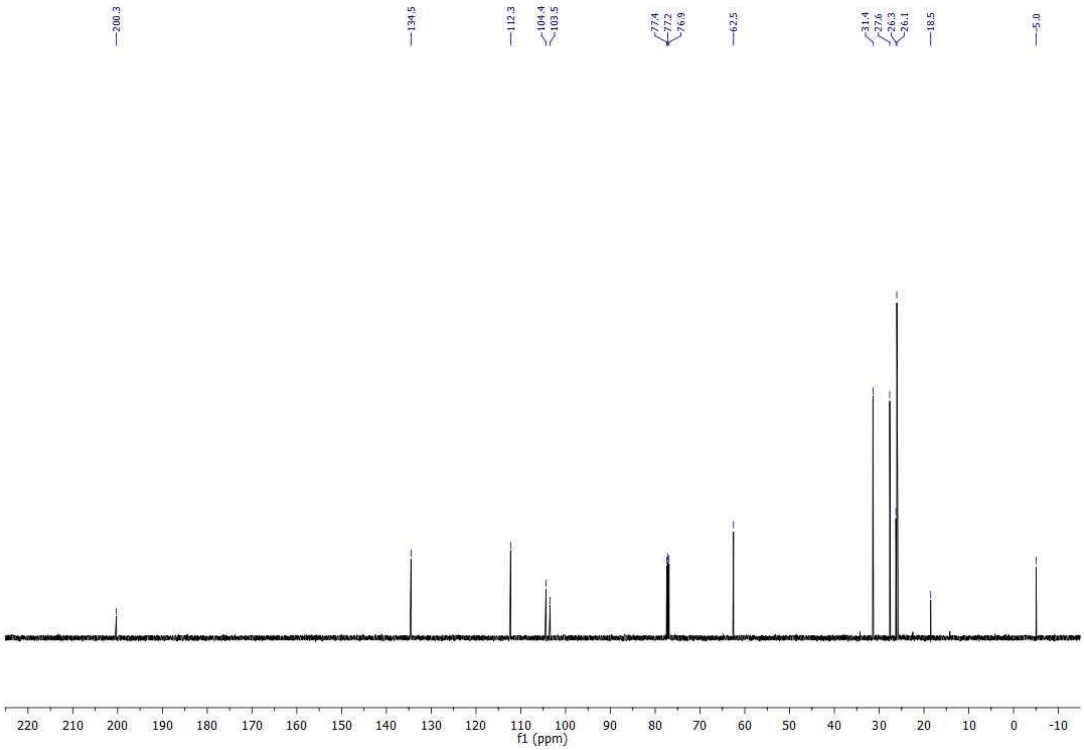

207.0
100.0
83.3
77.4
77.2
76.9
63.2
30.8
27.5
26.4
26.1
24.9
18.5
-4.9
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

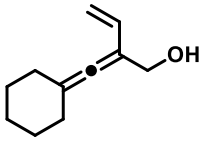

O
MeO
O
OTBS

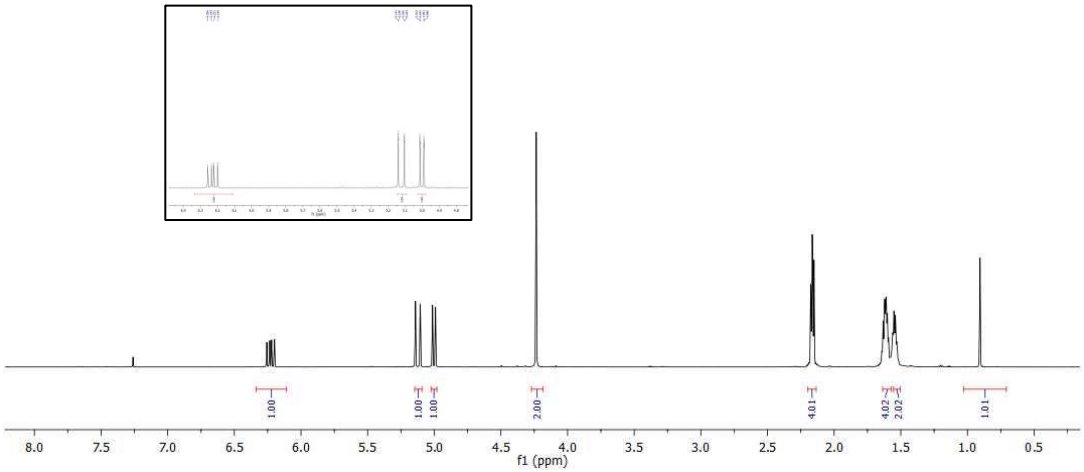

2.00
3.00
2.00
2.00
4.01
2.00
9.03
5.95
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

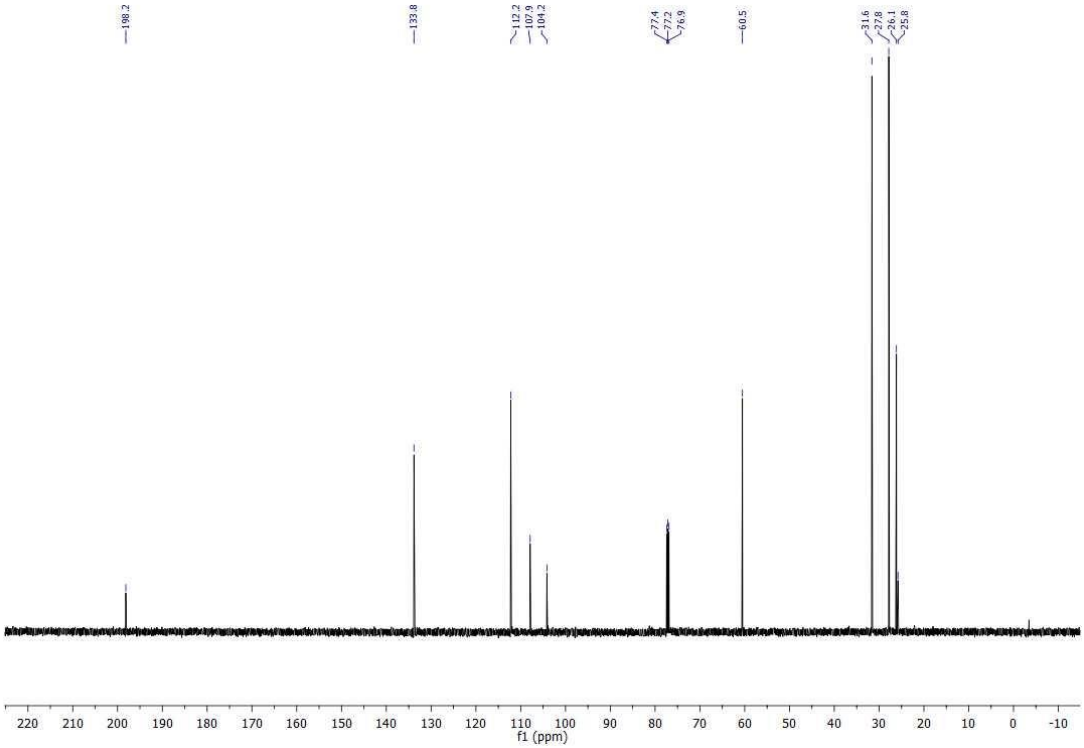

153.4
85.4
84.1
77.8
77.4
77.2
76.9
54.3
51.9
37.0
25.9
25.2
22.7
18.3
-5.0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

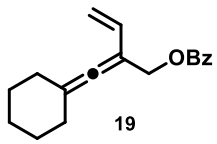

OTBS
0.96
1.00
1.00
2.00
4.02
6.00
9.02
6.00
f1 (ppm)


200.3
134.5
112.3
104.4
103.5
77.4
77.2
76.9
62.5
31.4
27.6
26.3
26.1
18.5
-5.0
f1 (ppm)

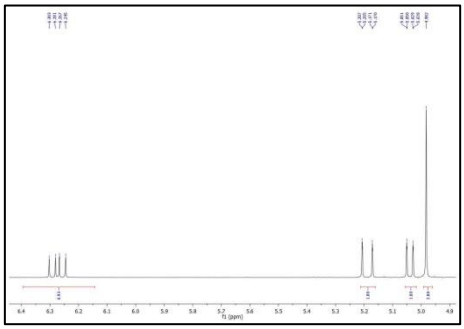

OH

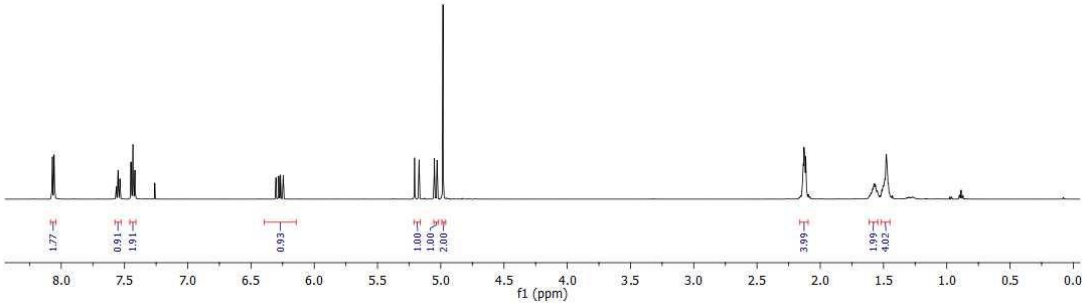

1.00
1.00
1.00
2.00
4.01
4.02
2.02
1.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

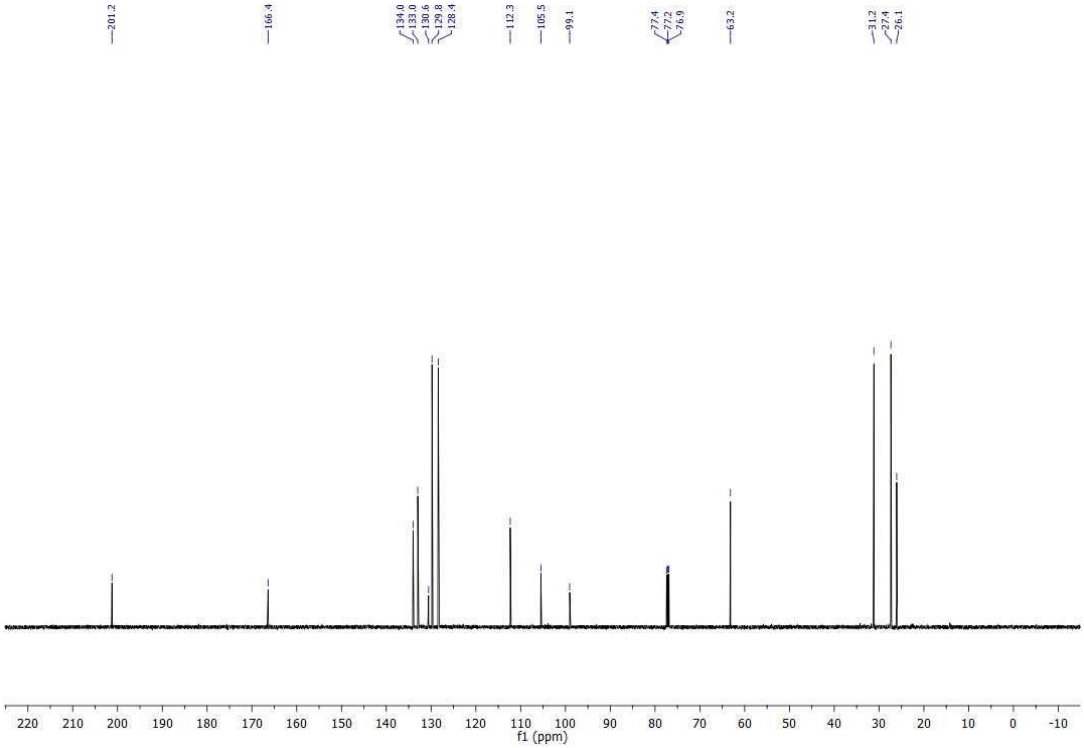

198.2
133.8
112.2
107.9
104.2
77.4
77.2
76.9
60.5
31.6
27.8
26.1
25.8
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

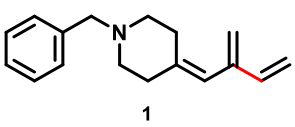

OBz

19

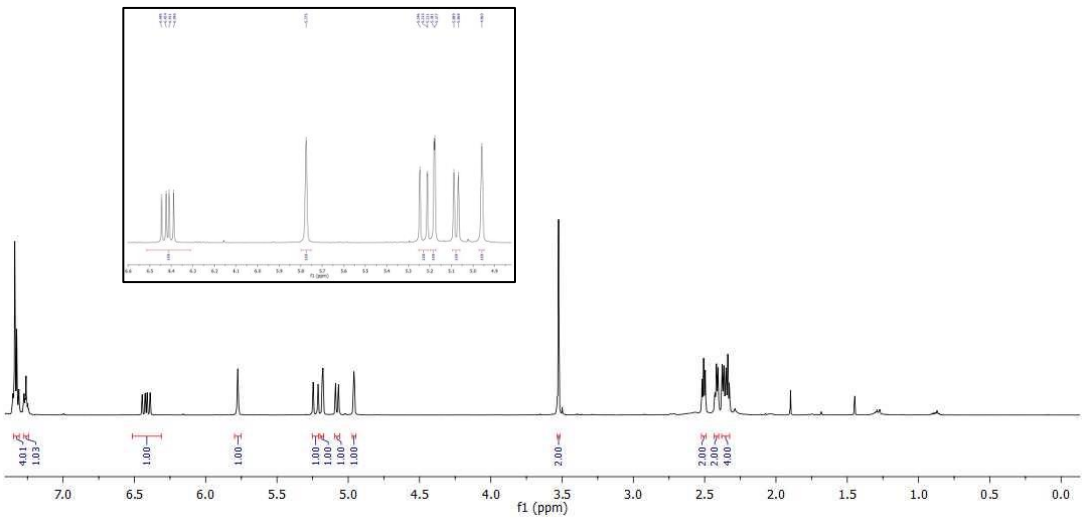


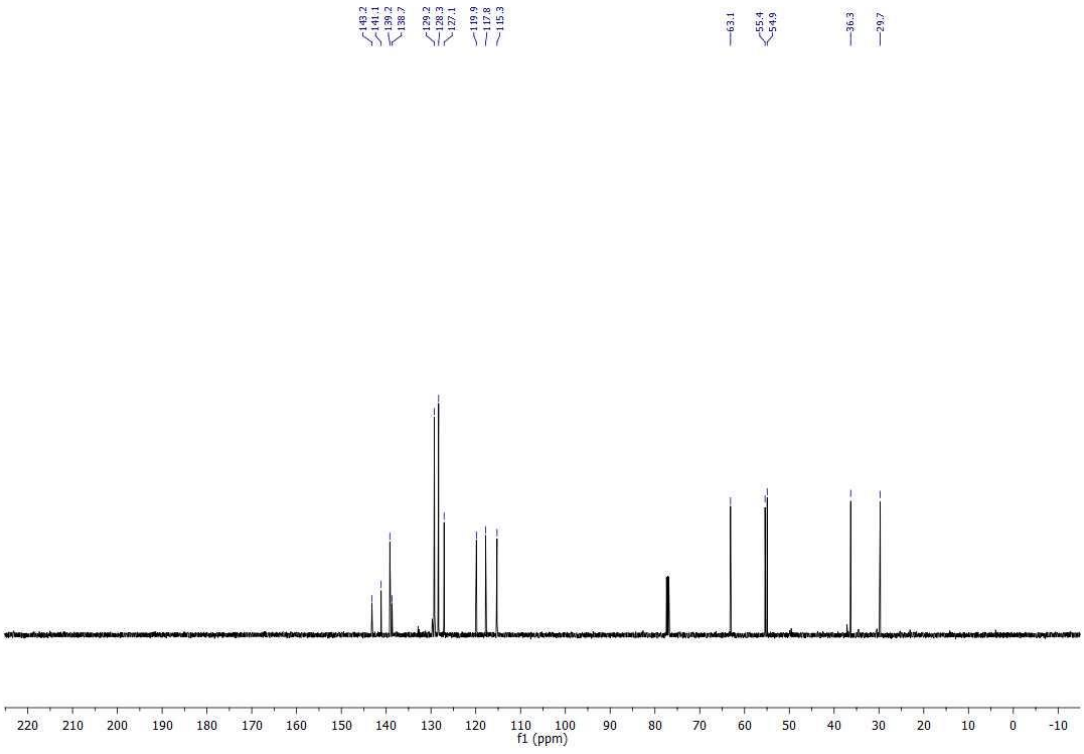

1.77
0.91
1.91
0.93
1.00
1.00
2.00
3.99
1.99
4.02
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

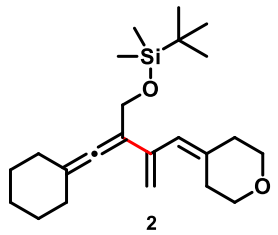

201.2
166.4
134.0
133.0
130.6
129.8
128.4
112.3
105.5
99.1
77.4
77.2
76.9
63.2
31.2
27.4
26.1
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



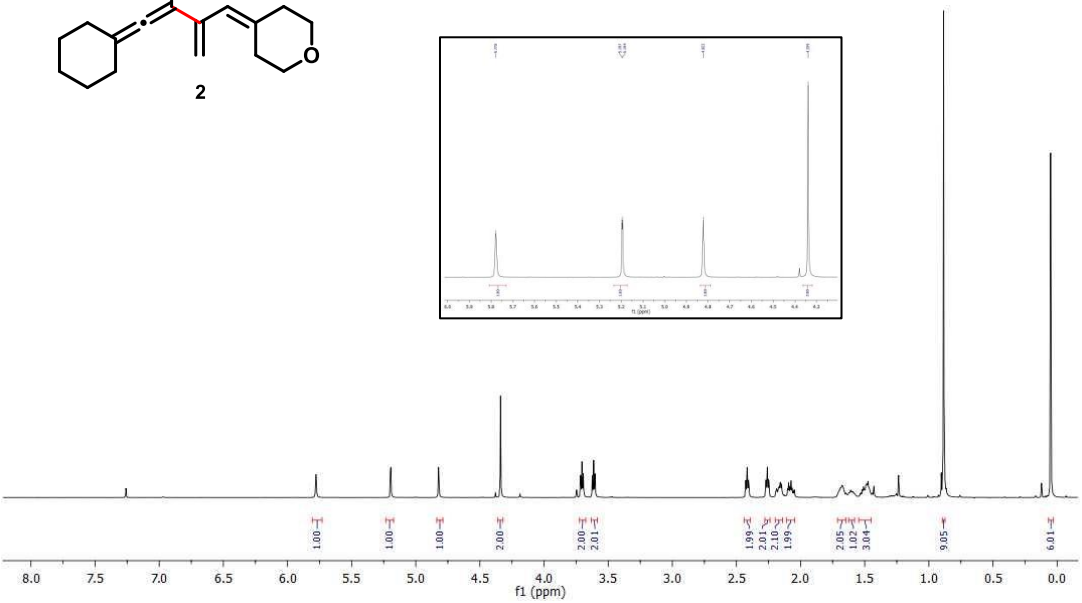
1

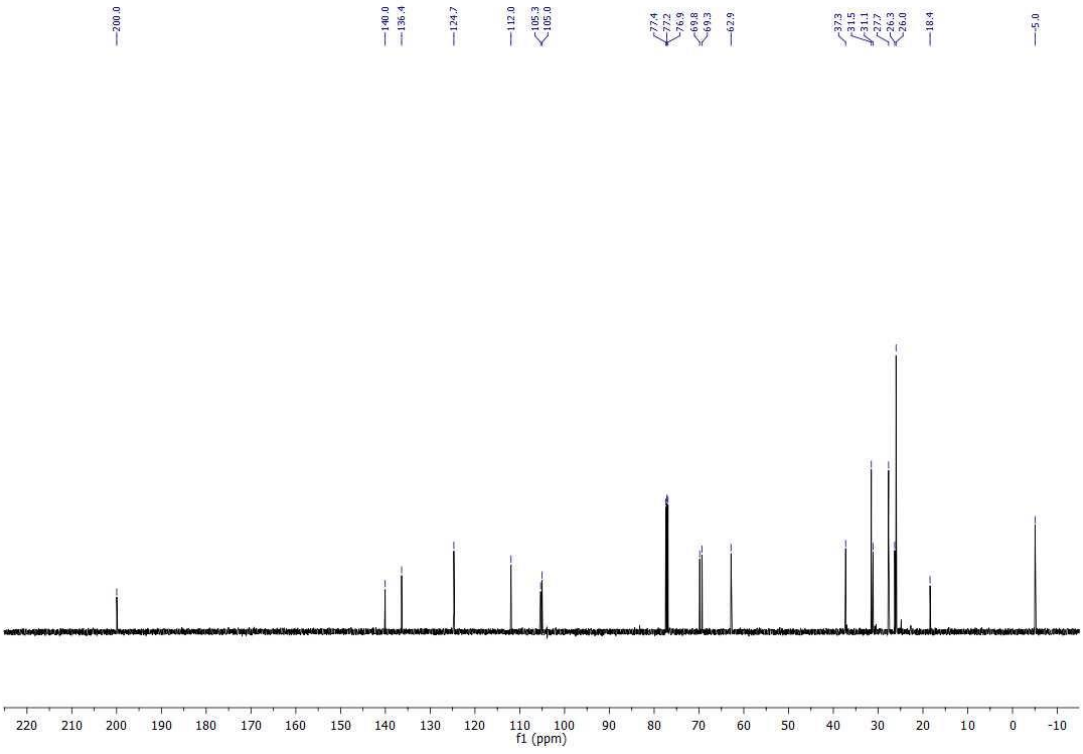

4.01
1.03
1.00
1.00
1.00
1.00
1.00
2.00
2.00
2.00
4.00
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

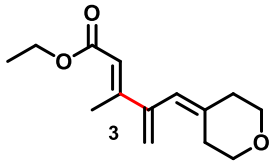

143.2
141.1
139.2
138.7
129.2
128.3
127.1
119.9
117.8
115.3
63.1
55.4
54.9
36.3
29.7
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

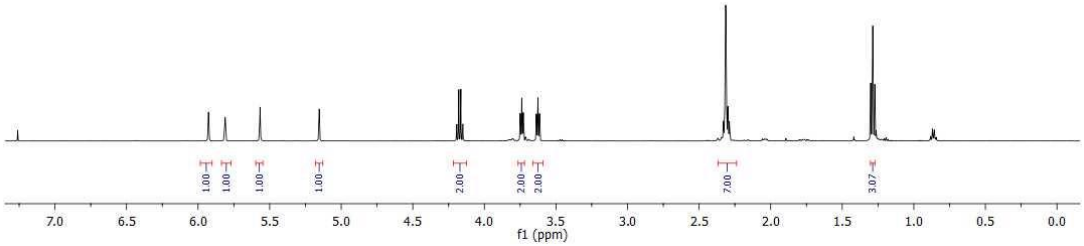

Si
O
O

2

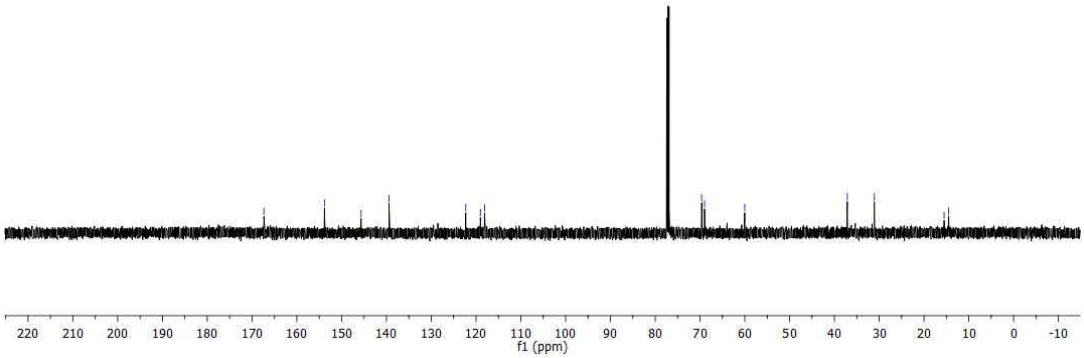

1.00
1.00
1.00
2.00
2.00
2.01
1.99
2.01
2.16
1.99
2.05
1.02
3.04
9.05
6.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

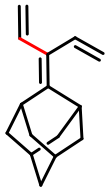

200.0
140.0
136.4
124.7
112.0
105.3
105.0
77.4
77.2
76.9
69.8
69.3
62.9
37.3
31.5
31.1
27.7
26.3
26.0
18.4
-5.0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
3
O

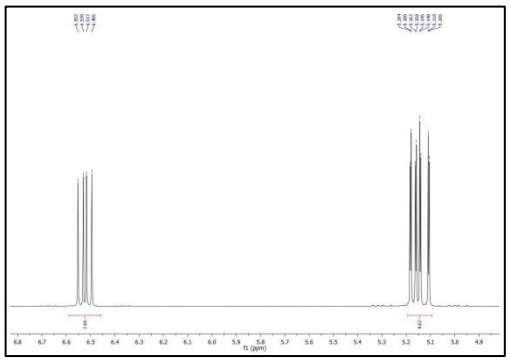

1.00
1.00
1.00
1.00
2.00
2.00
2.00
7.00
3.07
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

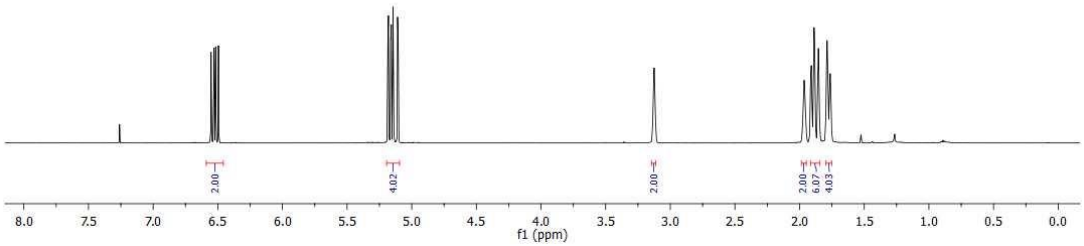

167.4
153.8
145.7
139.4
122.3
119.0
118.1
69.6
69.0
60.0
37.1
31.1
15.5
14.5

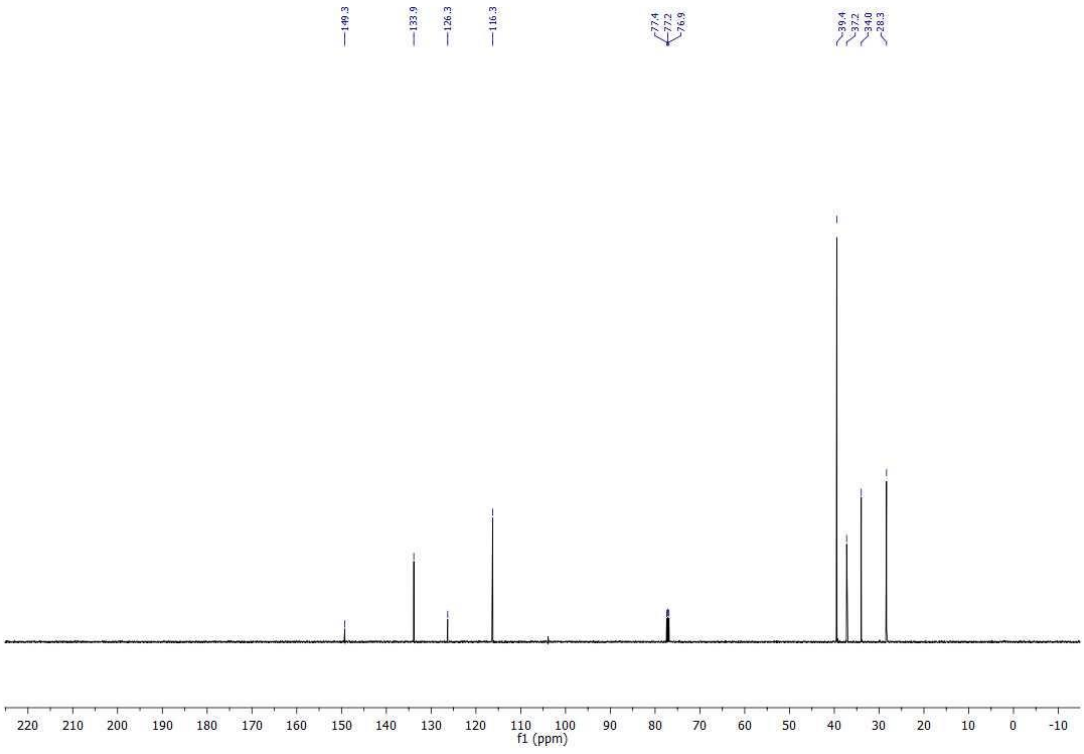

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

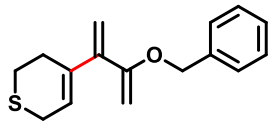


4

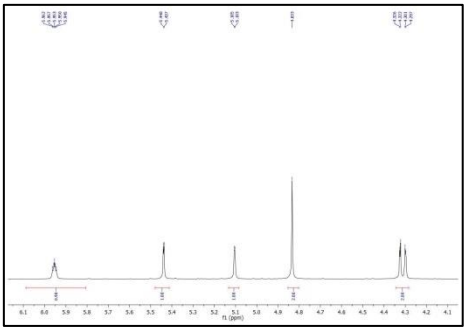


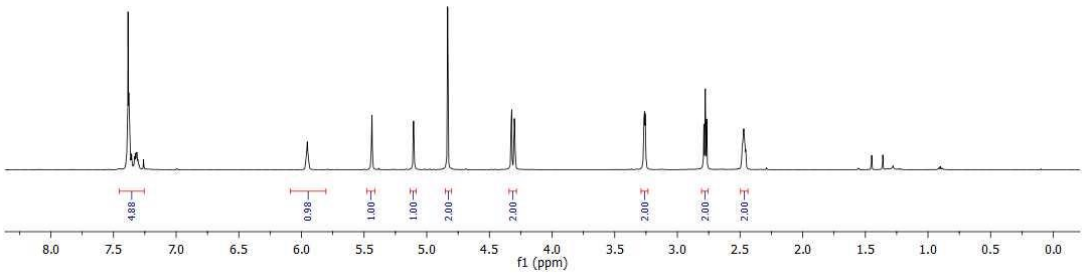

2.00
4.02
2.00
2.00
6.07
4.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

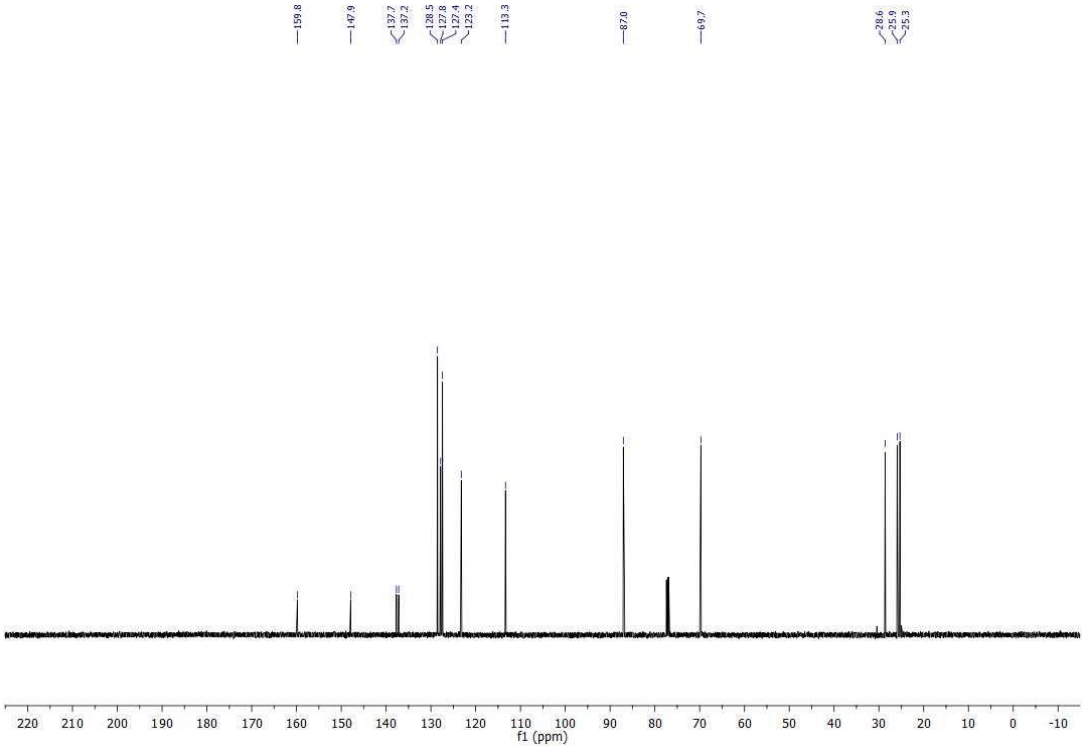

149.3
133.9
126.3
116.3
77.4
77.2
76.9
39.4
37.2
34.0
28.3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

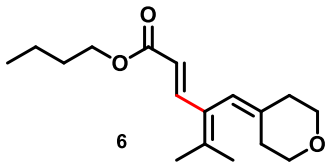

S
O

5

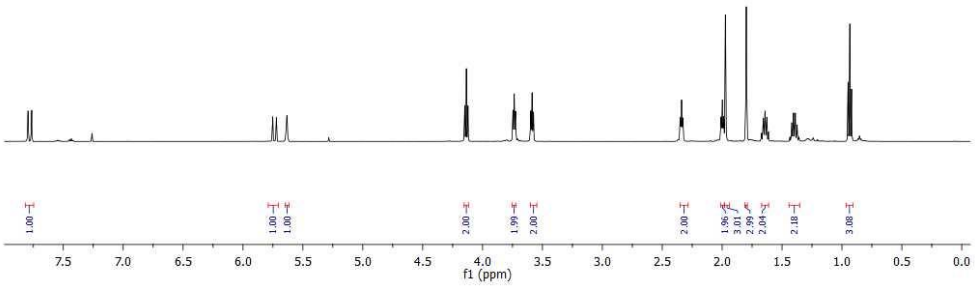


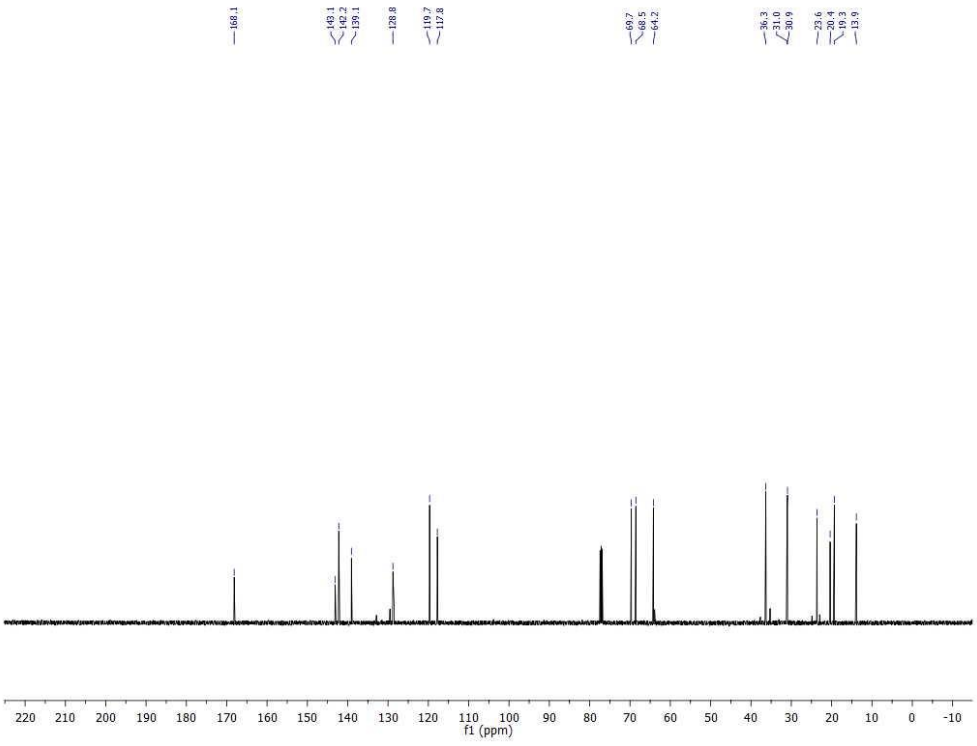

4.88
0.98
1.00
1.00
2.00
2.00
2.00
2.00
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

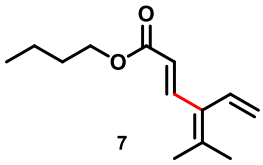

159.8
147.9
137.7
137.2
128.5
127.8
127.4
123.2
113.3
87.0
69.7
28.6
25.9
25.3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
O

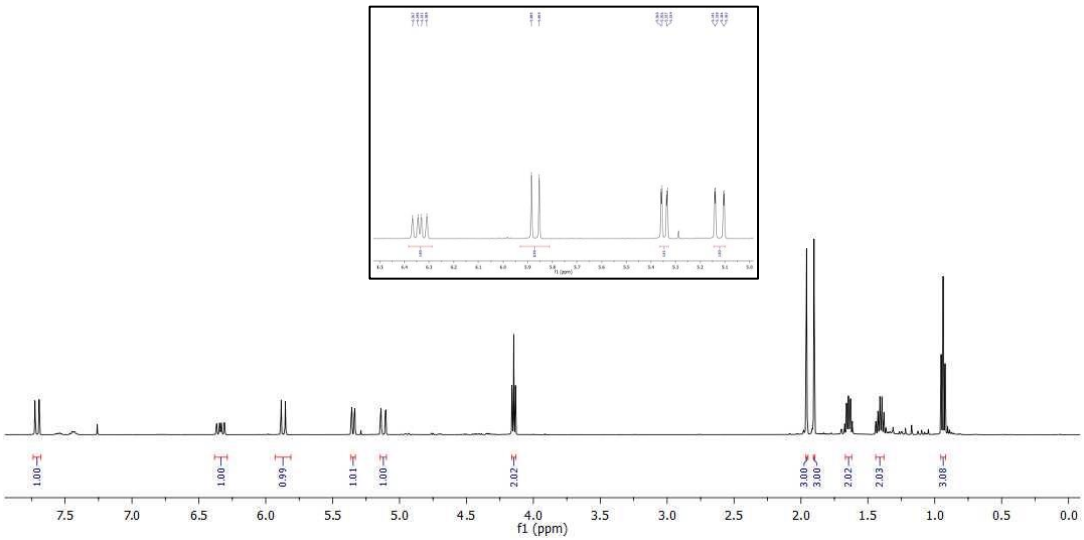
6

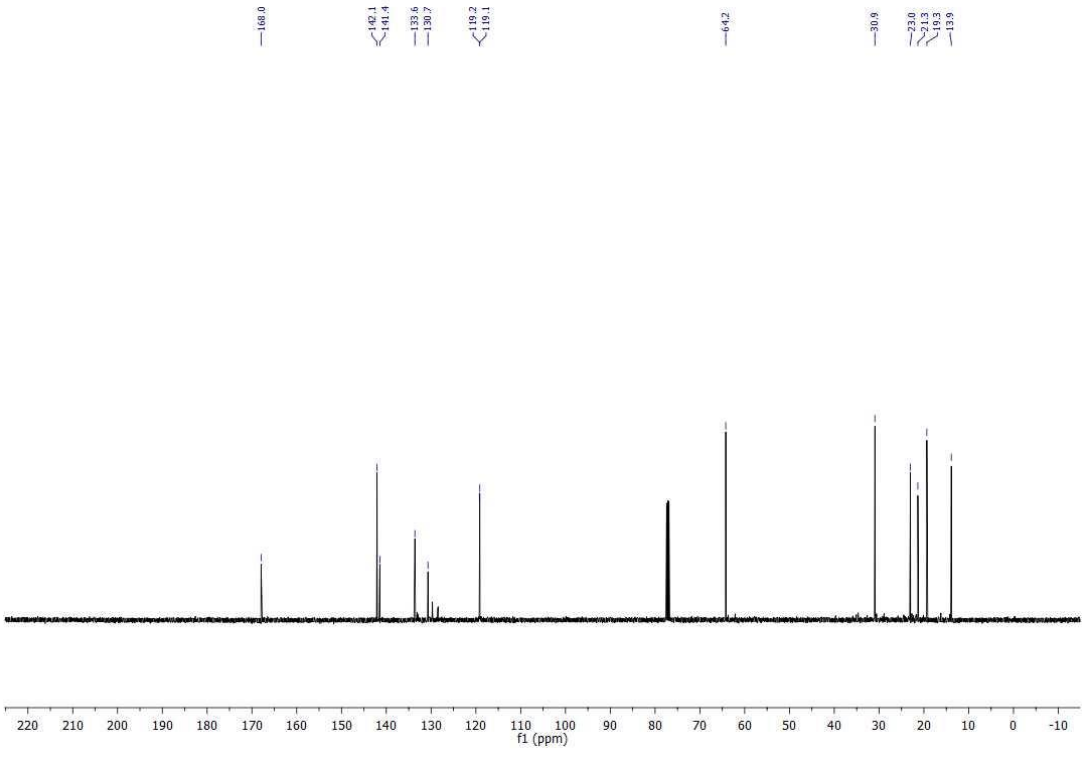

1.00
1.00
1.00
2.00
1.99
2.00
2.00
1.96
3.01
2.99
2.04
2.18
3.08
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

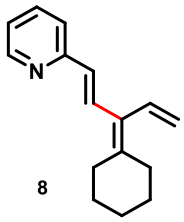

168.1
143.1
142.2
139.1
120.8
119.7
117.8
69.7
68.5
64.2
36.3
31.0
30.9
23.6
20.4
19.3
13.9
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O

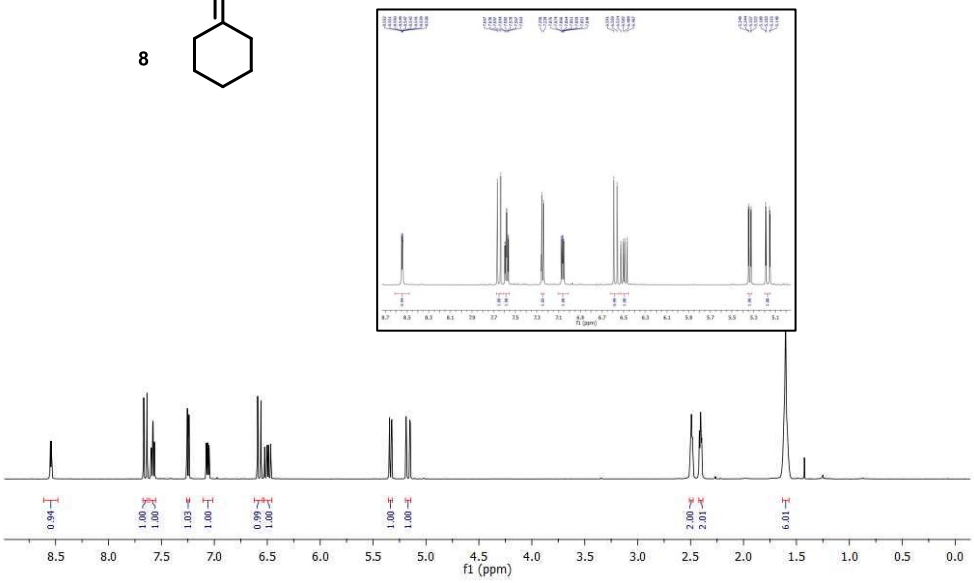
7

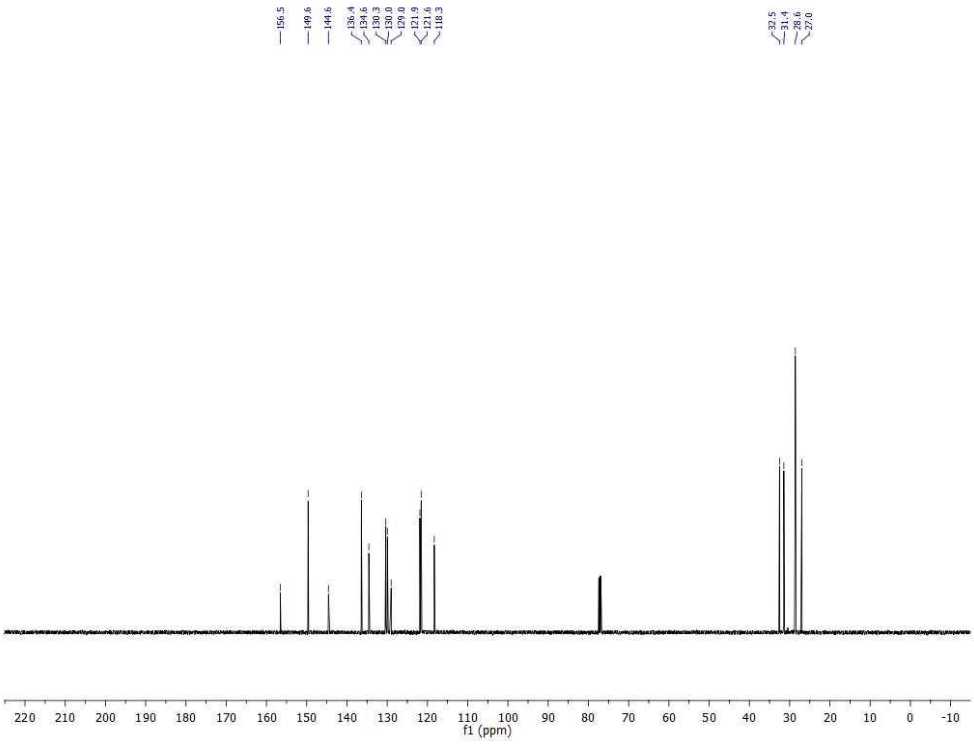

1.00
1.00
0.99
1.01
1.00
2.02
3.00
3.00
2.02
2.03
3.08
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

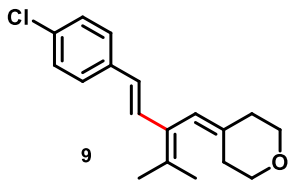

168.0
142.1
141.4
133.6
130.7
119.2
119.1
64.2
30.9
23.0
21.3
19.3
13.9
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


N

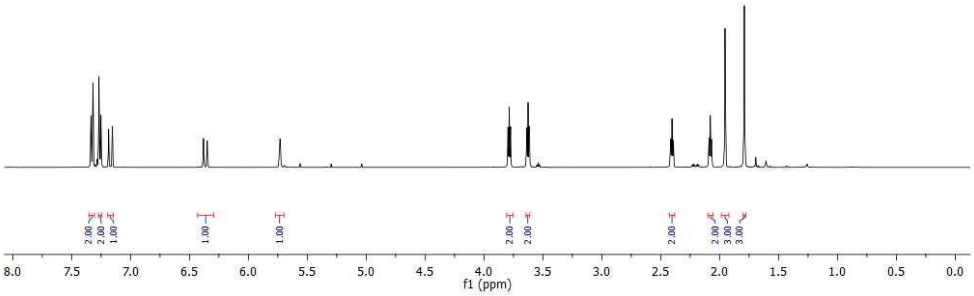
8

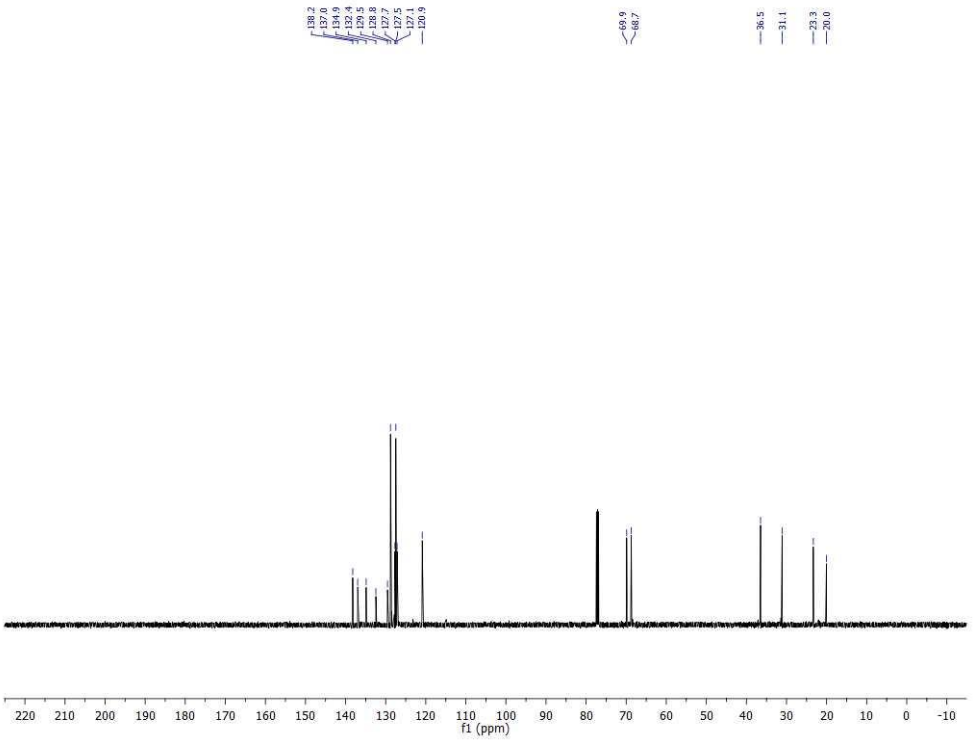

0.94
1.00
1.00
1.03
1.00
0.99
1.00
1.00
1.00
2.00
2.01
6.01
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

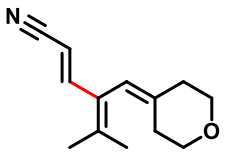

156.5
149.6
144.6
136.4
134.6
130.3
130.0
129.0
121.9
121.6
118.3
32.5
31.4
28.6
27.0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Cl
O

9


2.00
2.00
1.00
1.00
1.00
2.00
2.00
2.00
2.00
3.00
3.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


138.2
137.0
134.9
132.4
129.5
128.8
127.7
127.5
127.1
120.9
69.9
68.7
36.5
31.1
23.3
20.8
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



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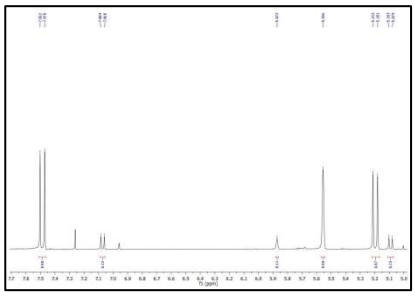
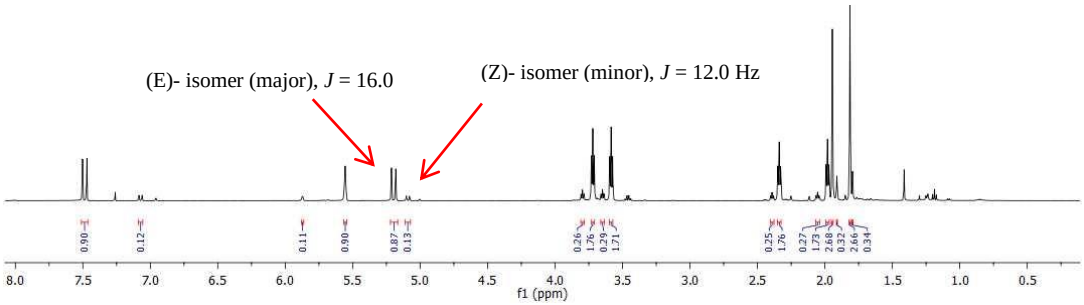
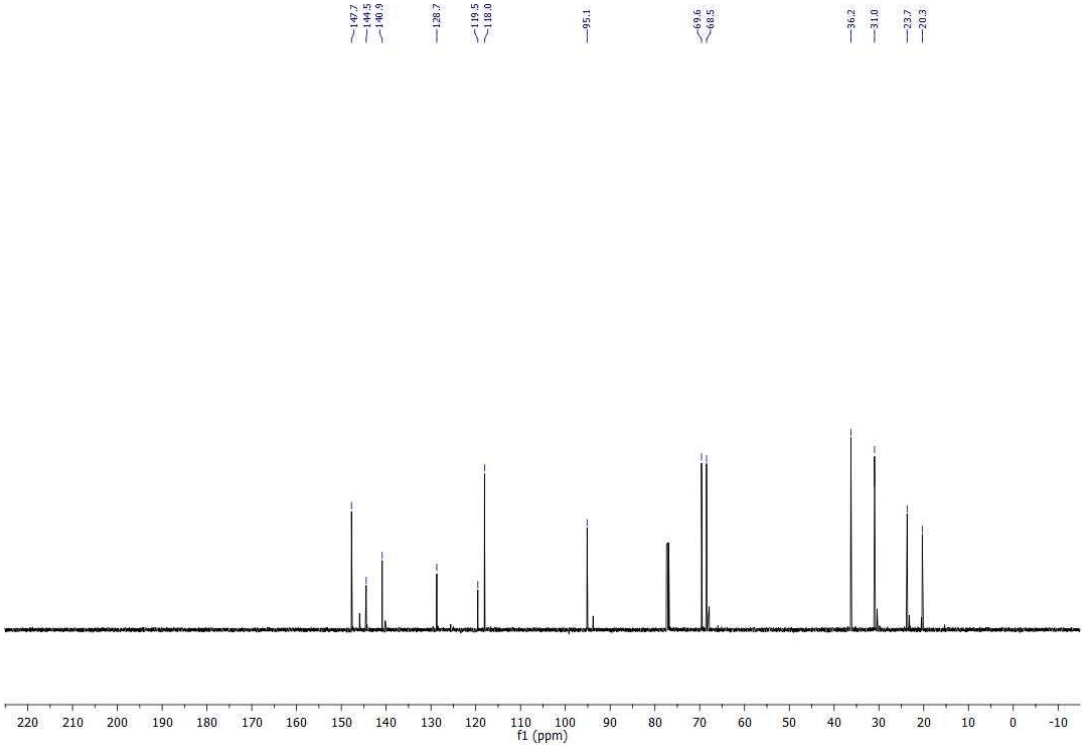
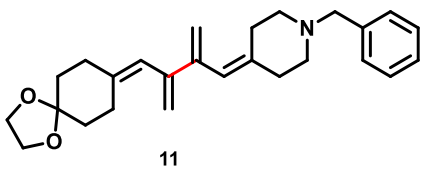
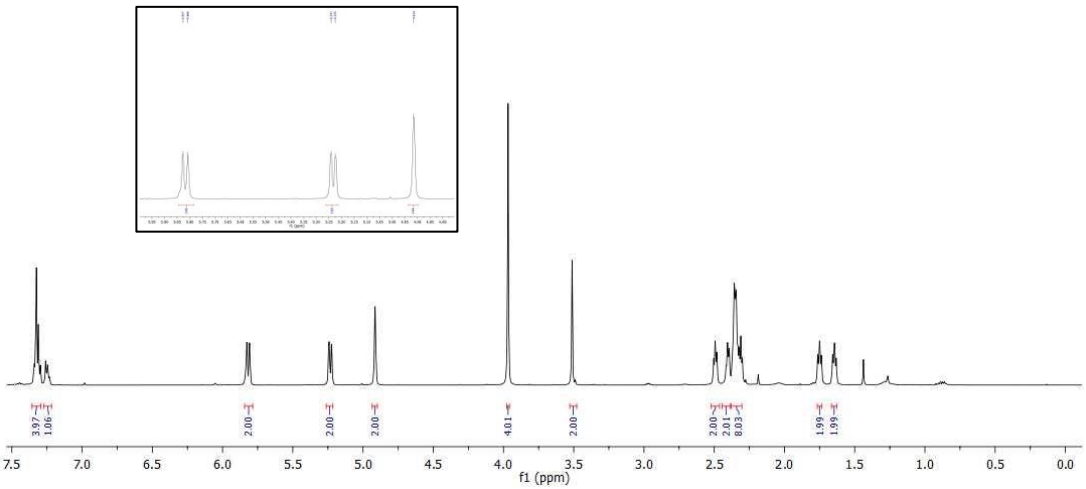




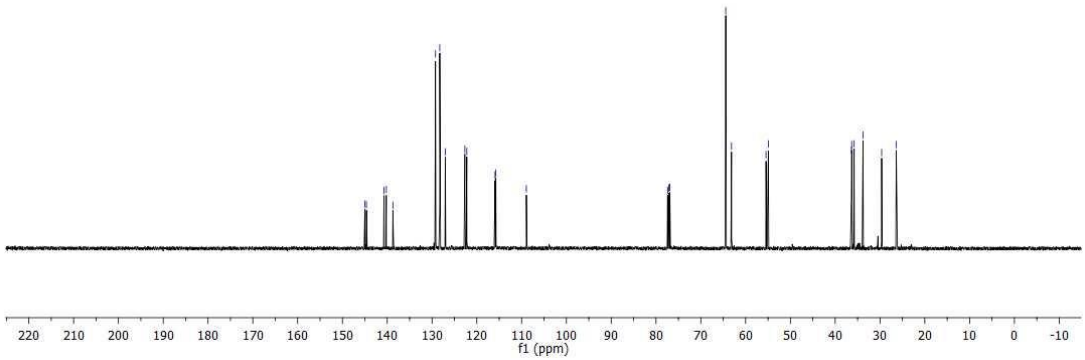


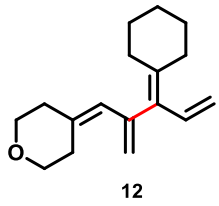

N
O
O

11

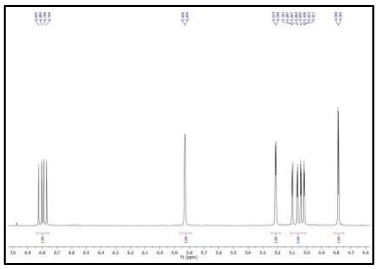

3.97
1.06
2.00
2.00
2.00
4.01
2.00
2.00
2.01
8.03
1.99
1.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

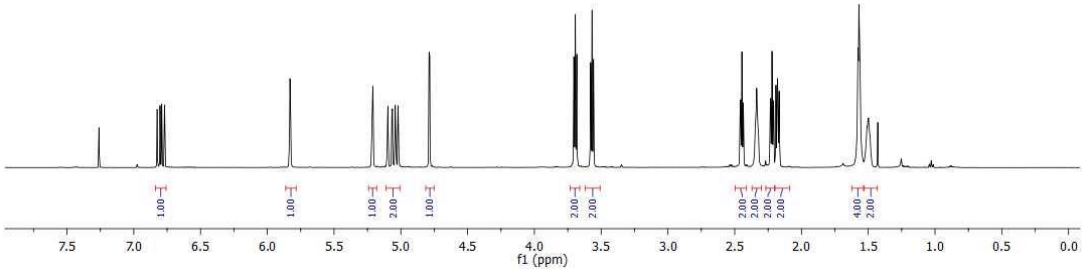

146.0
144.6
140.7
140.2
138.7
129.2
128.3
127.0
122.7
122.2
115.9
115.8
108.9
77.4
77.2
76.9
64.4
63.1
55.4
54.9
36.4
36.3
35.8
33.8
29.6
26.4

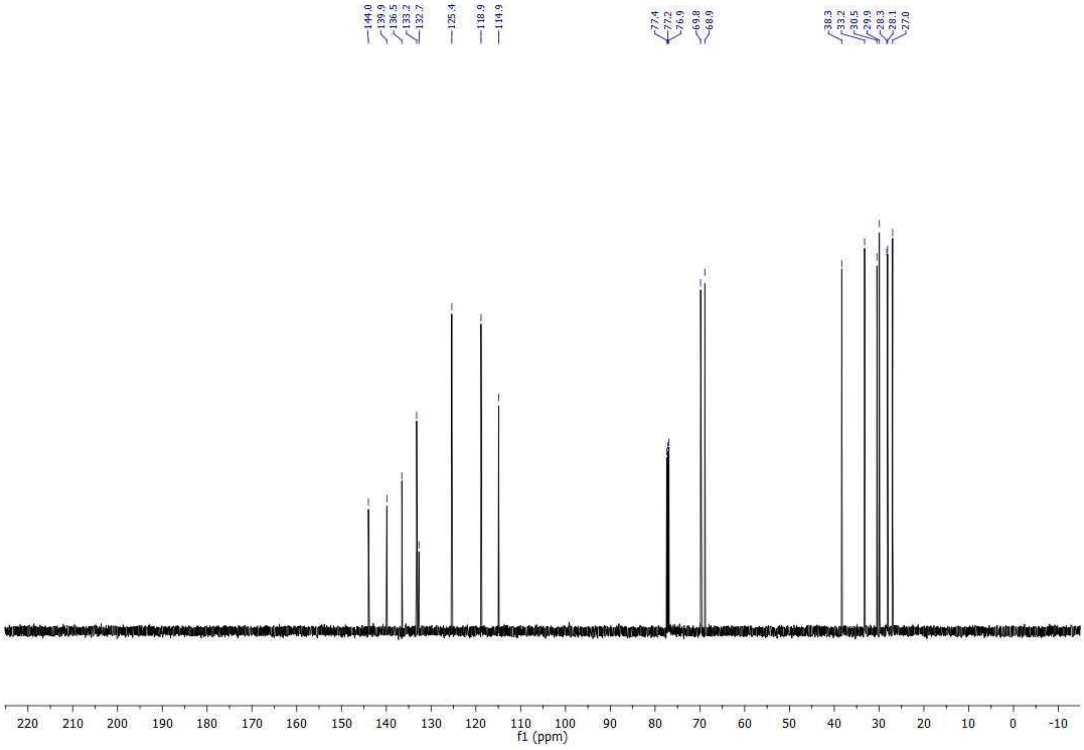

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

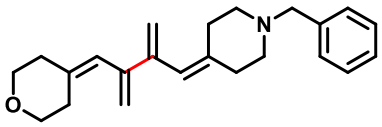

O

12

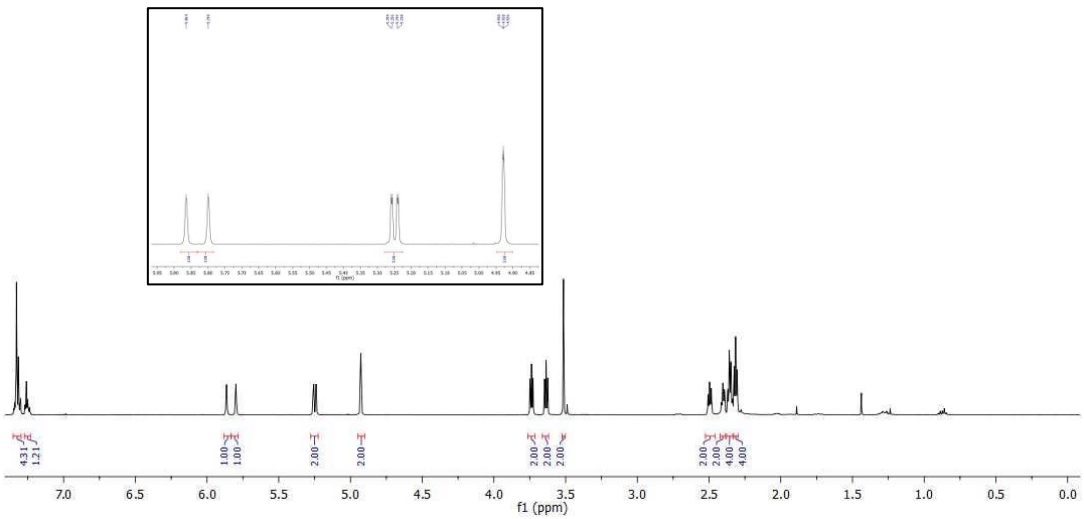


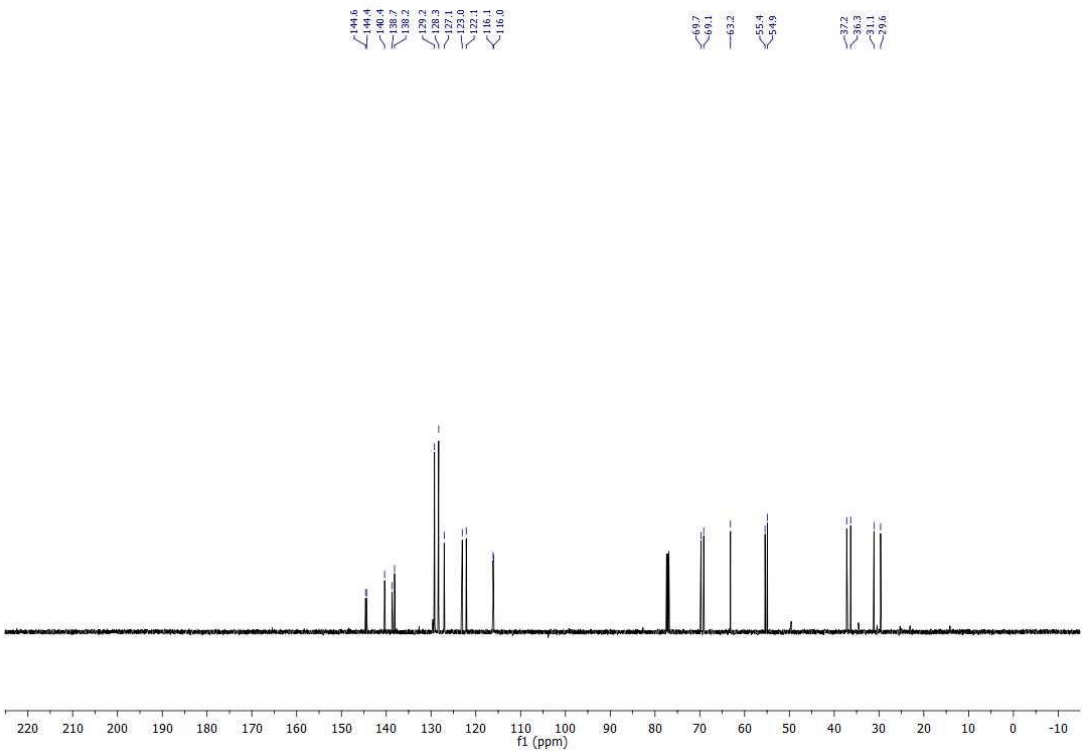

1.00
1.00
1.00
2.00
1.00
2.00
2.00
2.00
2.00
2.00
4.00
2.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

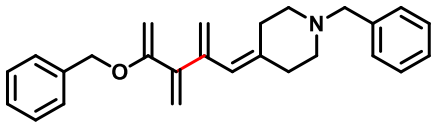

144.0
139.9
136.5
133.2
132.7
125.4
118.9
114.9
77.4
77.2
76.9
69.8
68.9
38.3
33.2
30.5
29.9
28.3
28.1
27.0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


N
O

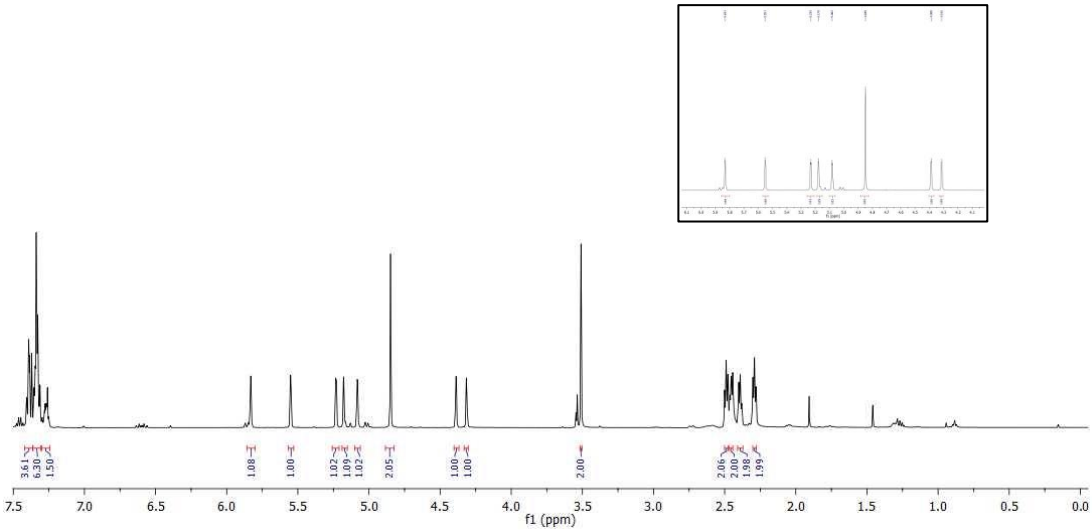
13

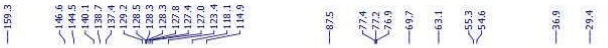

4.31
1.21
1.00
1.00
2.00
2.00
2.00
2.00
2.00
2.00
4.00
4.00
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

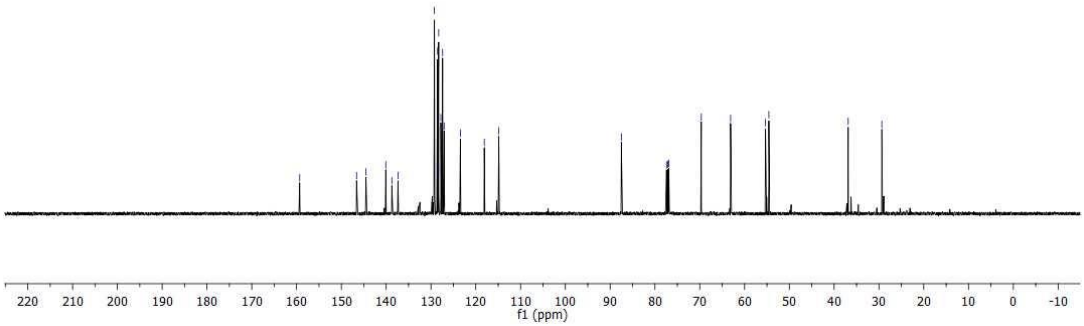

144.6
144.4
140.4
138.7
138.2
129.2
128.3
127.1
125.0
122.1
116.1
116.0
69.7
69.1
63.2
55.4
54.9
37.2
36.3
31.1
29.6
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

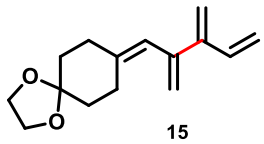

O
N

14

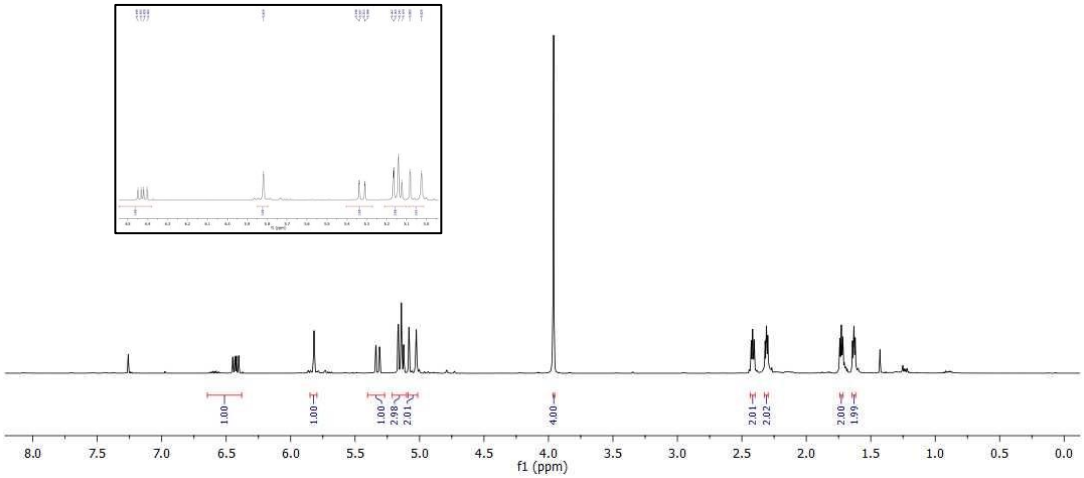

3.61
6.30
1.50
1.08
1.00
1.02
1.09
1.02
2.05
1.00
1.00
2.00
2.06
2.00
1.98
1.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


159.3
146.6
144.5
140.1
138.7
137.4
129.2
128.5
128.3
128.3
127.8
127.4
127.0
123.4
110.1
114.9
87.5
77.4
77.2
76.9
69.7
63.1
55.3
54.6
36.9
29.4

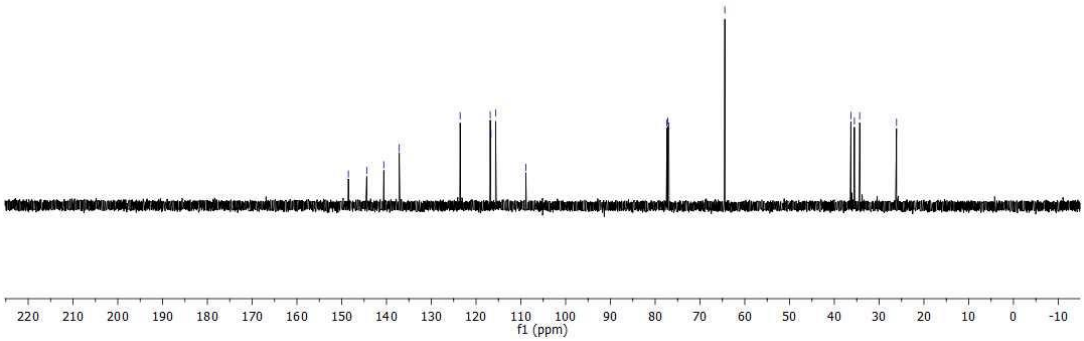

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

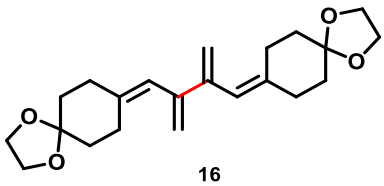


15

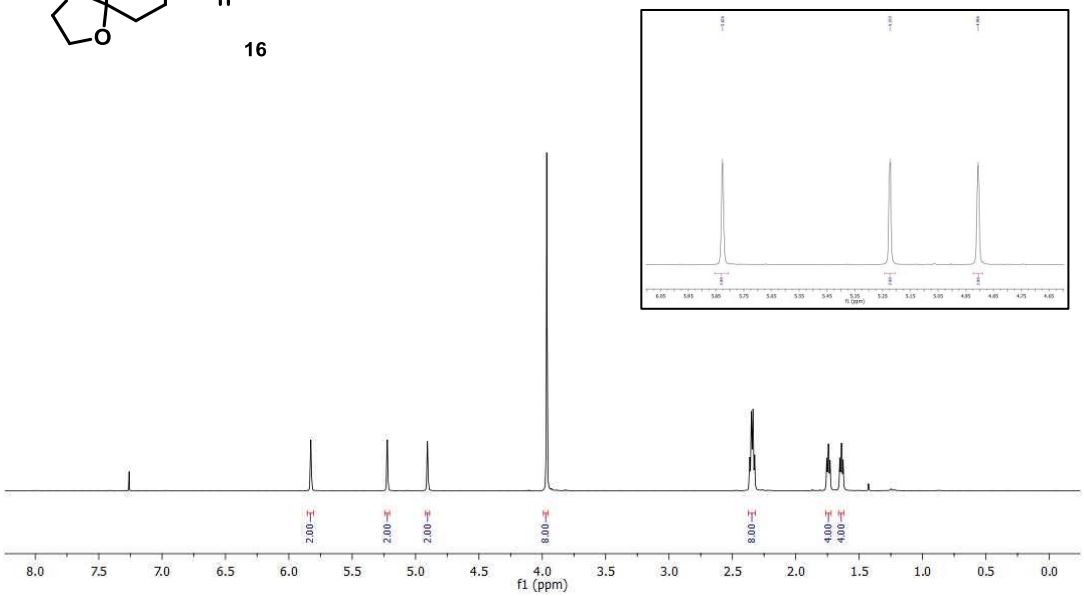

1.00
1.00
1.00
2.98
2.01
4.00
2.01
2.02
2.00
1.90
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

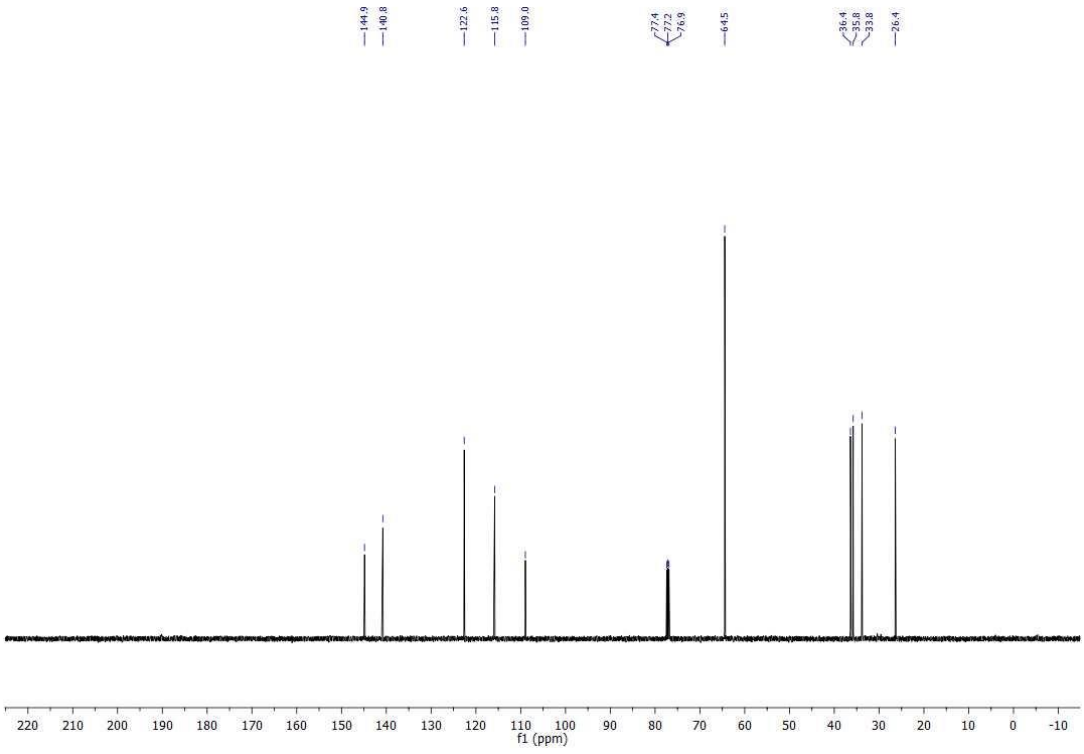

148.5
144.4
140.6
137.2
123.6
116.8
116.7
115.6
108.9
77.4
77.2
76.9
64.5
36.3
35.5
34.3
26.1

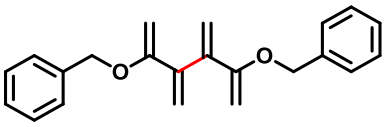

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
O
O

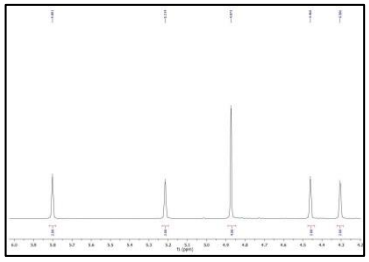
16

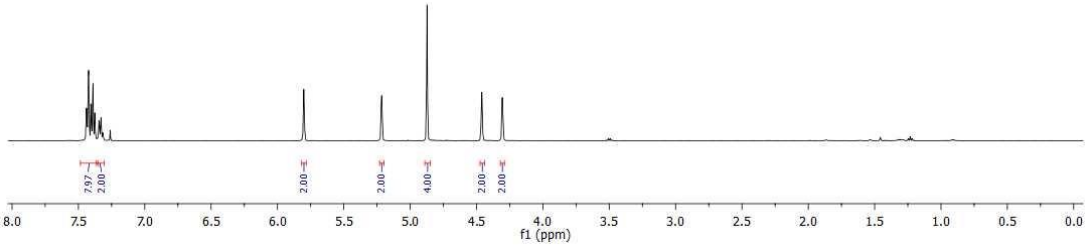

2.00
2.00
2.00
8.00
8.00
4.00
4.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

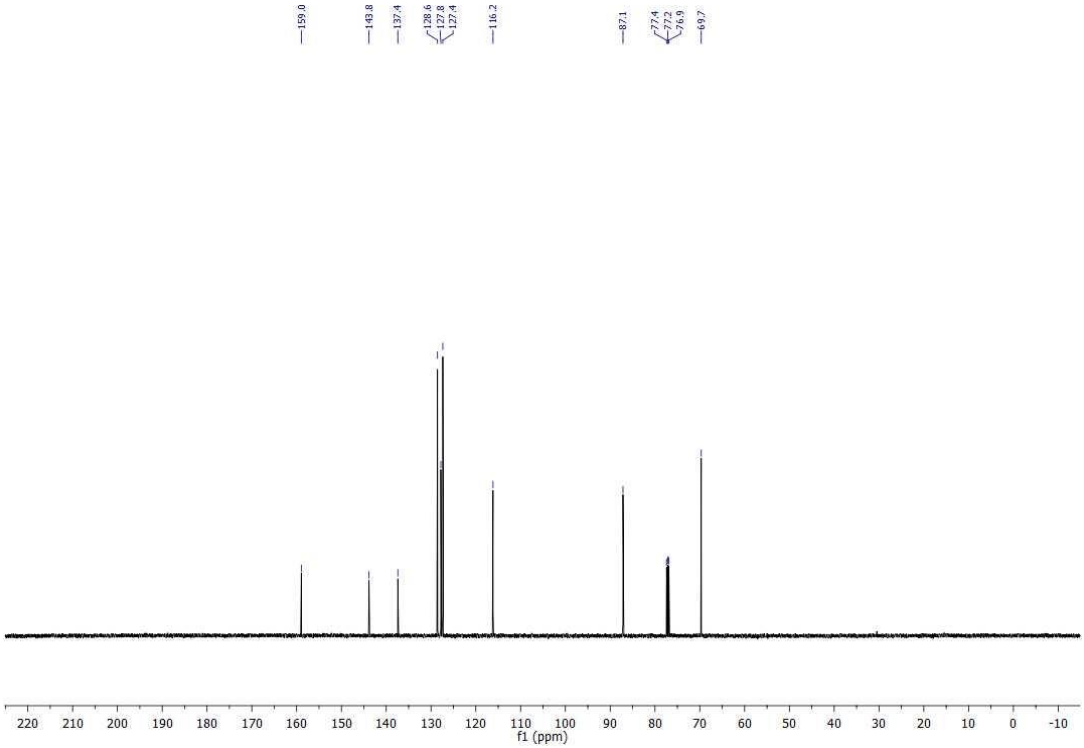

144.9
140.8
122.6
115.8
109.0
77.4
77.2
76.9
64.5
36.4
35.8
33.8
26.4
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

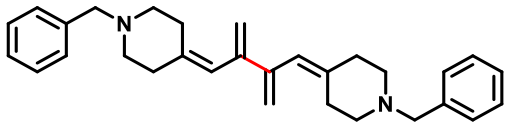


17

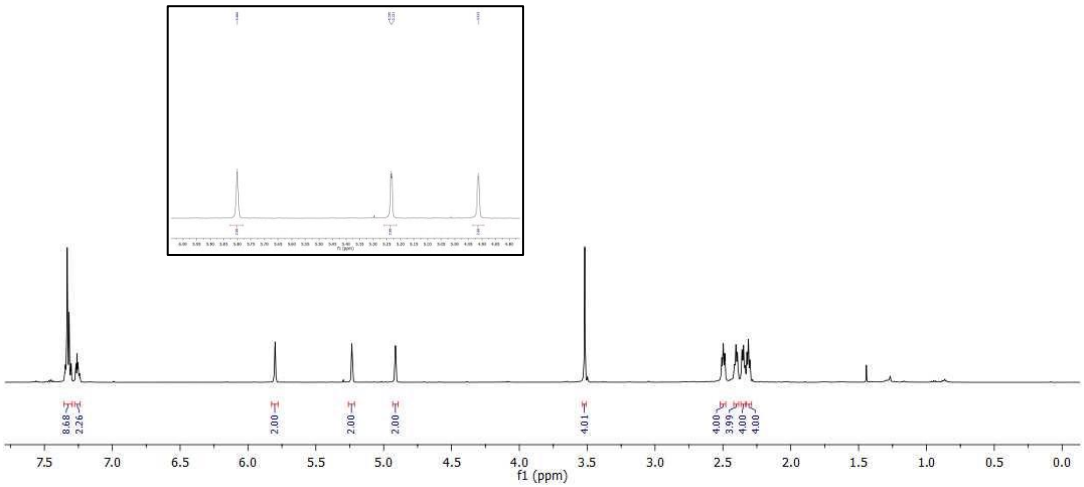


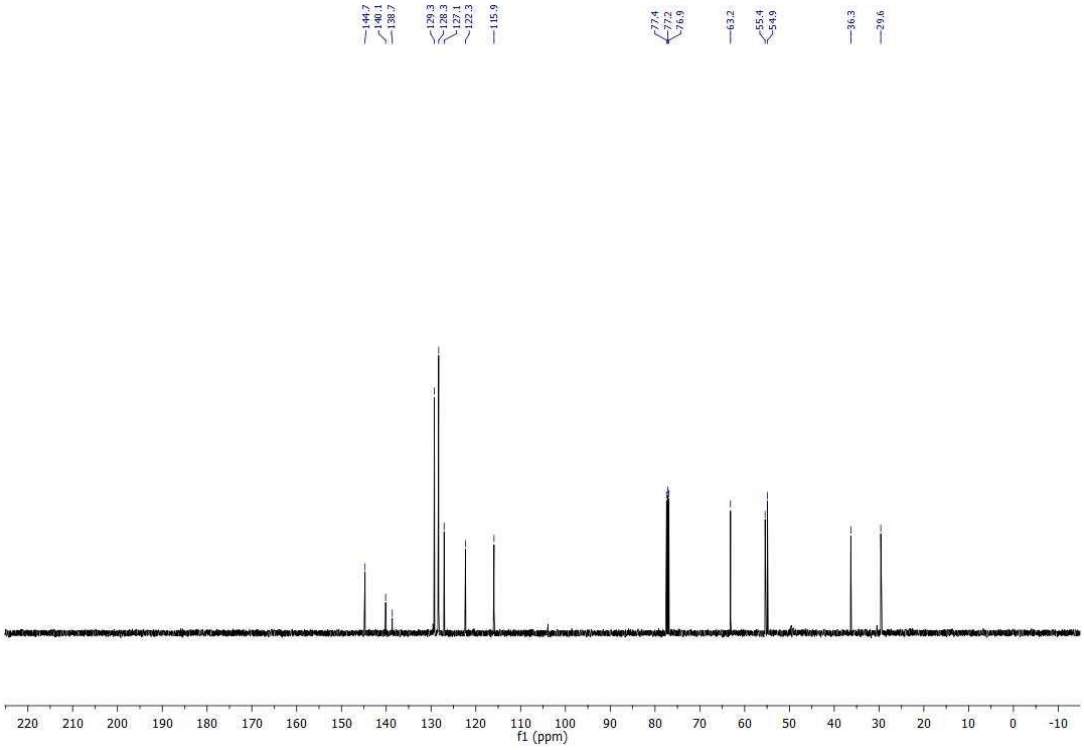

7.97
2.00
2.00
2.00
4.00
2.00
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

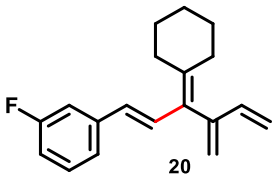

159.0
143.8
137.4
128.6
127.8
127.4
116.2
87.1
77.4
77.2
76.9
69.7
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



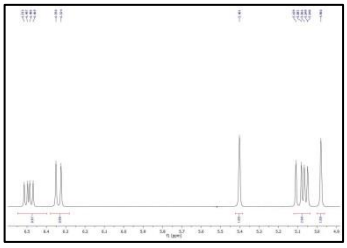
18

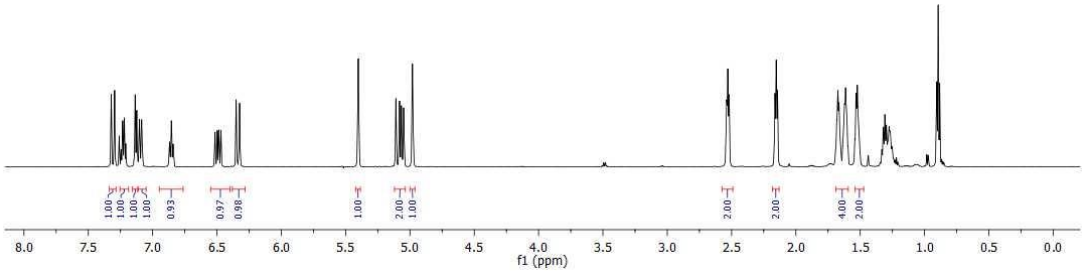

8.68
2.26
2.00
2.00
2.00
4.01
4.00
3.99
4.00
4.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


144.7
140.1
138.7
129.3
128.3
127.1
122.3
115.9
77.4
77.2
76.9
63.2
55.4
54.9
36.3
39.6
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

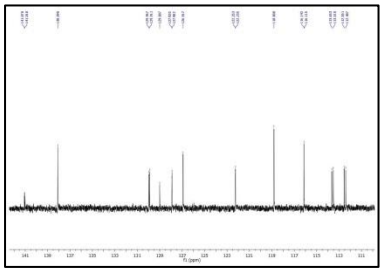

F

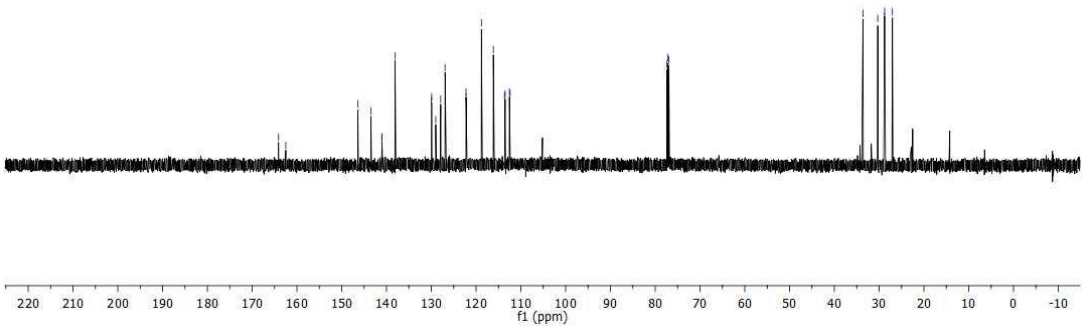
20

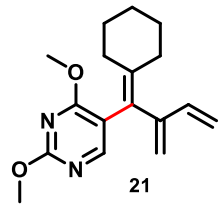



1.00
1.00
1.00
1.00
0.93
0.97
0.98
1.00
2.00
1.00
2.00
2.00
4.00
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

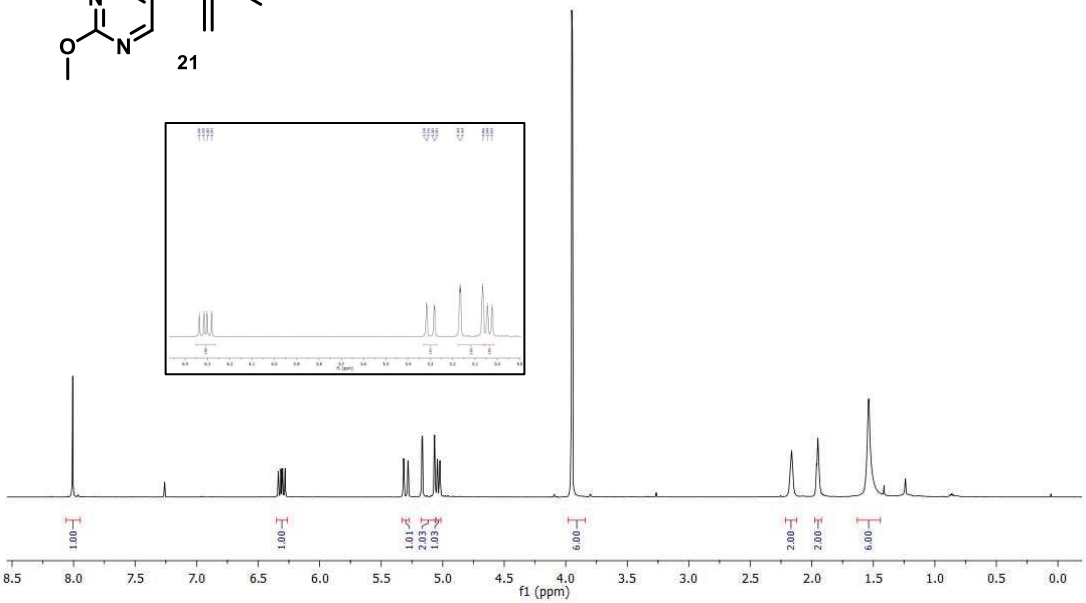

164.1
162.5
146.4
143.5
141.1
141.0
138.1
130.0
129.9
129.0
127.9
127.9
126.9
122.3
122.2
118.8
116.1
116.1
113.7
113.5
112.6
112.4
77.4
77.2
76.9
33.6
30.3
28.8
28.8
27.0

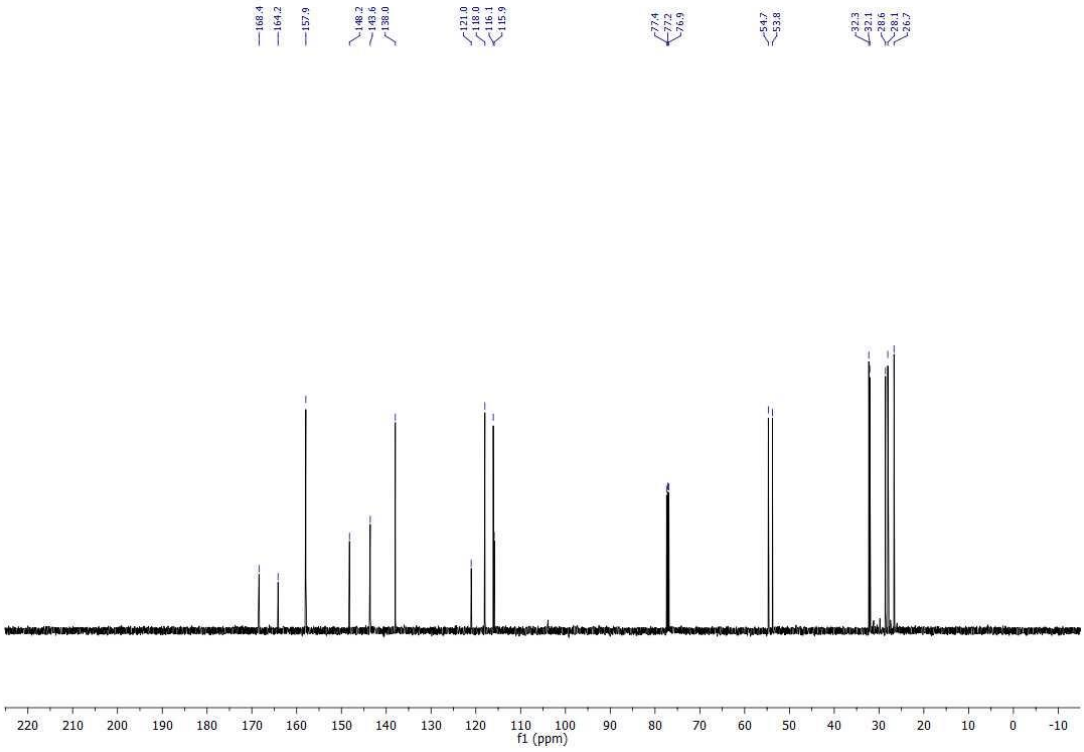


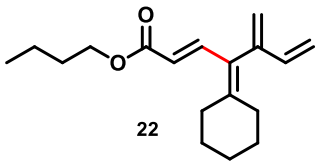

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
N
N
O

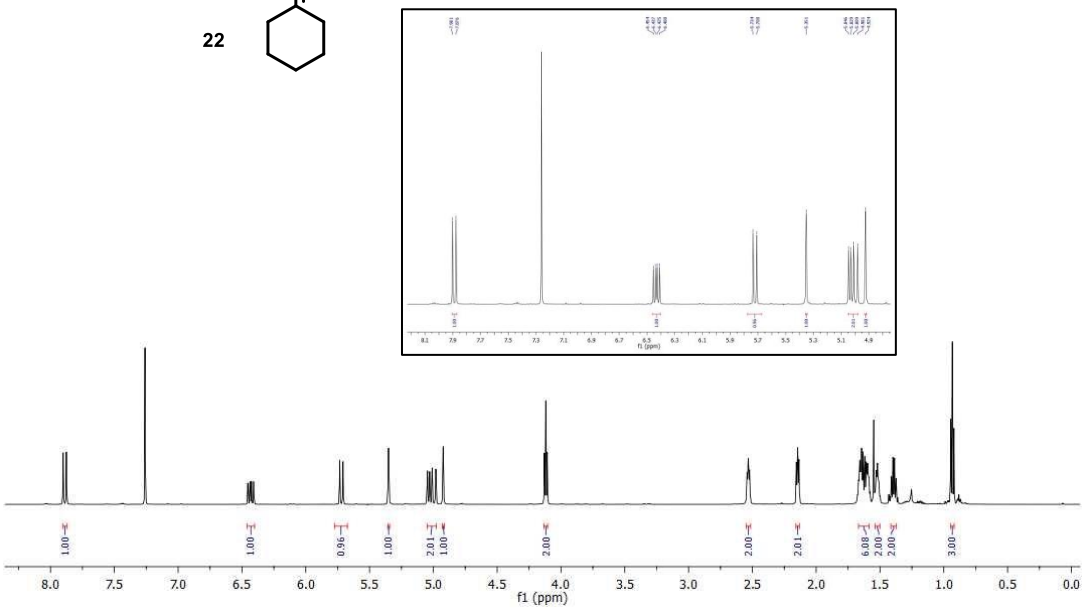
21

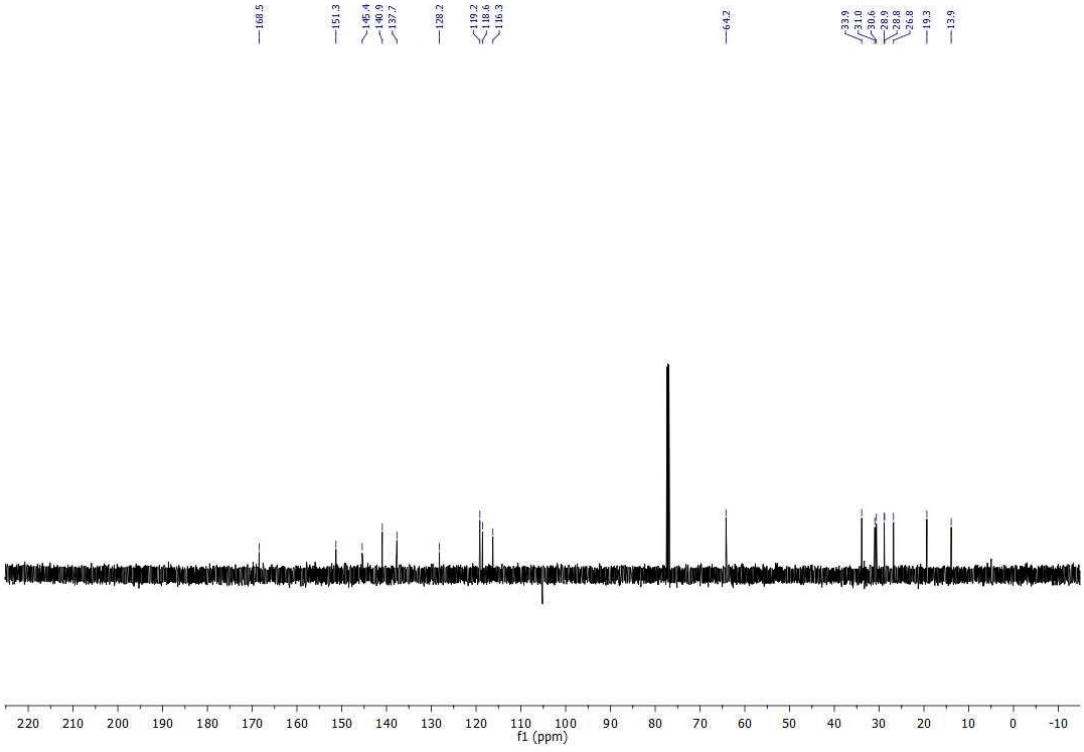

1.00
1.00
1.01
2.03
1.03
6.00
2.00
2.00
6.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

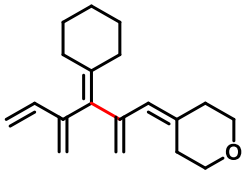

168.4
164.2
157.9
148.2
143.6
138.0
121.0
118.0
116.1
115.9
77.4
77.2
76.9
54.7
53.8
32.3
32.1
28.6
28.1
26.7
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



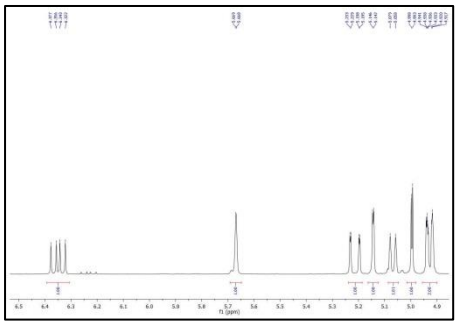
22

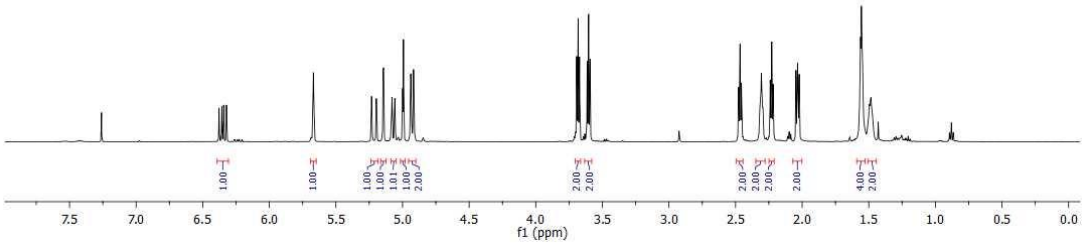

1.00
1.00
0.96
1.00
2.01
1.00
2.00
2.00
2.01
6.08
2.00
2.00
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


168.5
151.3
146.4
140.9
137.7
128.2
119.2
118.6
116.3
64.2
33.9
31.0
30.6
28.9
28.8
26.8
19.3
13.9
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

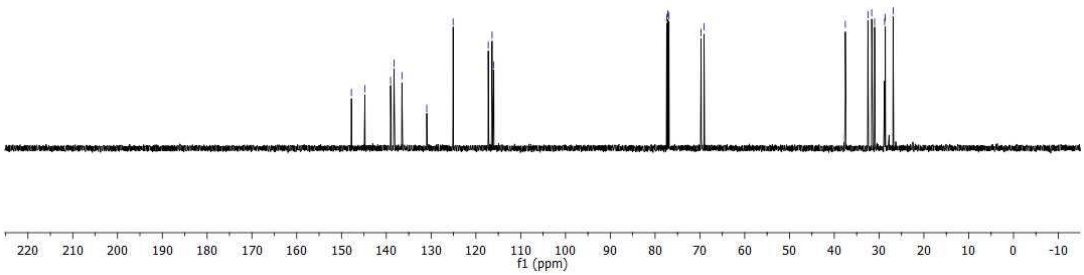


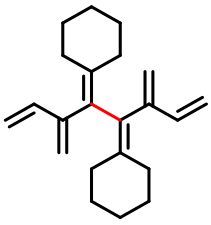
23



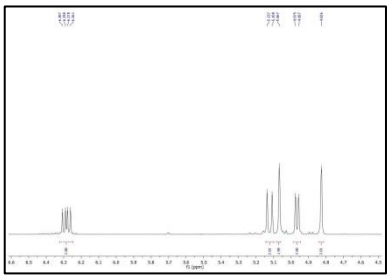

1.00
1.00
1.00
1.01
1.00
2.00
2.00
2.00
2.00
2.00
2.00
4.00
2.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

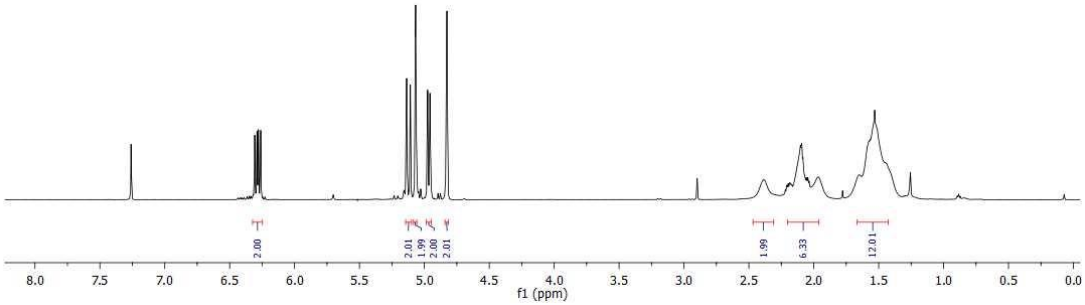

147.8
144.8
139.1
138.3
136.5
131.0
125.1
117.2
116.4
116.0
77.4
77.2
76.9
69.7
69.1
37.5
32.5
31.6
31.0
29.8
28.6
26.9


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

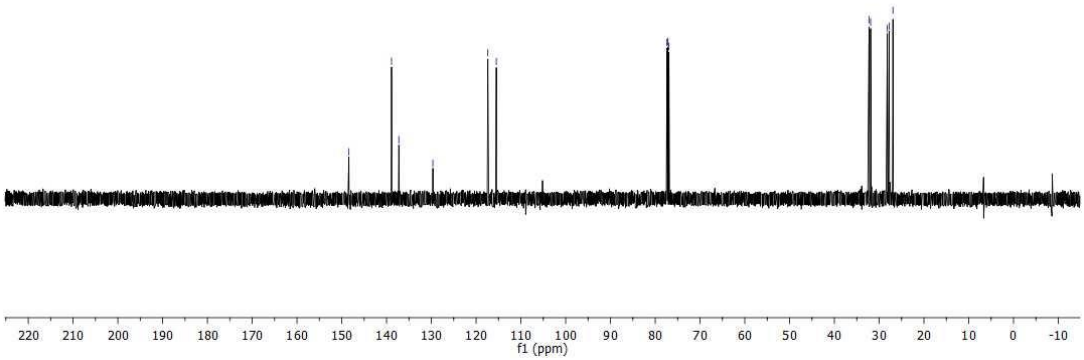


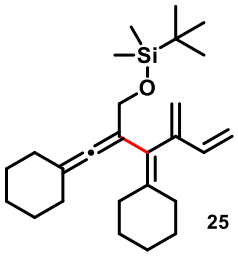
24



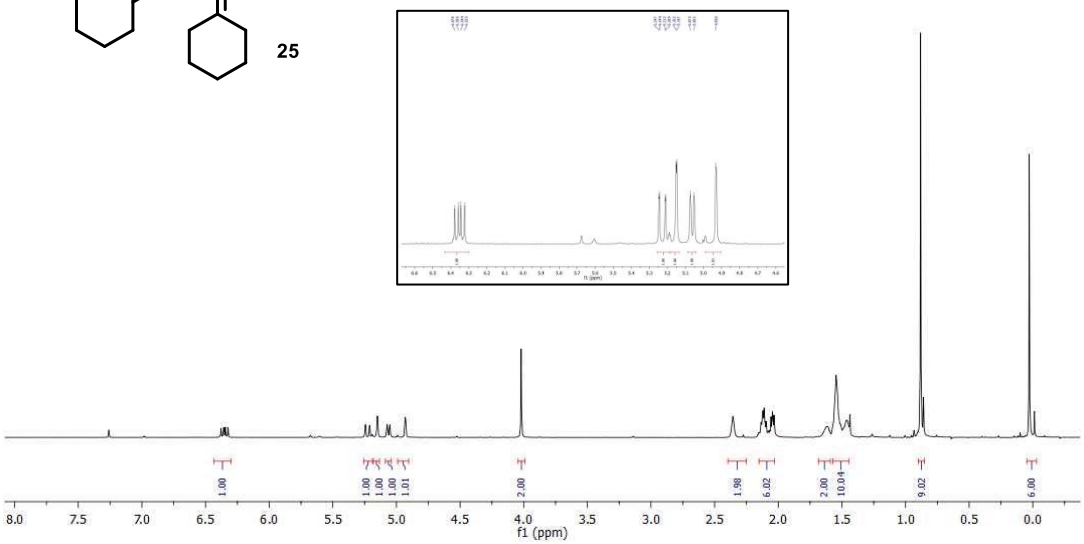

2.00
2.01
1.99
2.00
2.01
1.99
6.33
12.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


148.4
138.9
137.3
129.7
117.4
115.5
77.4
77.2
76.9
32.3
31.9
28.2
27.8
26.9

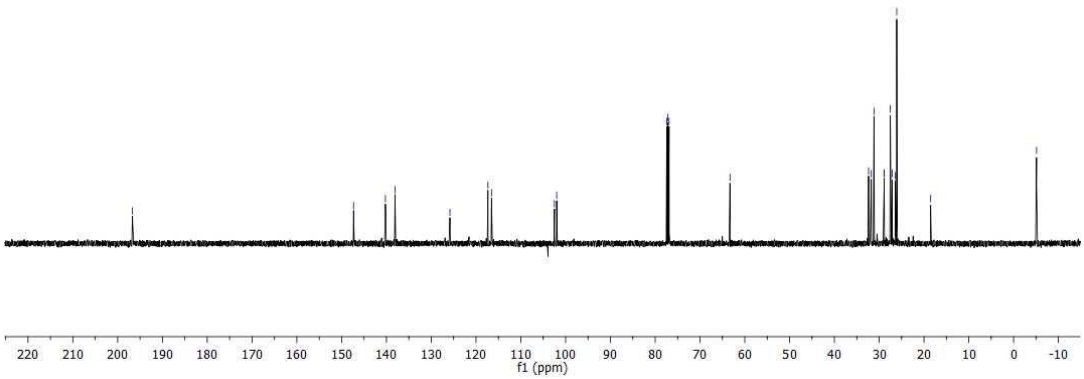

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

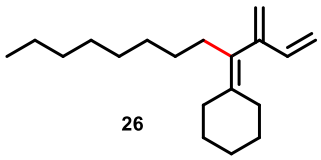

Si
O

25

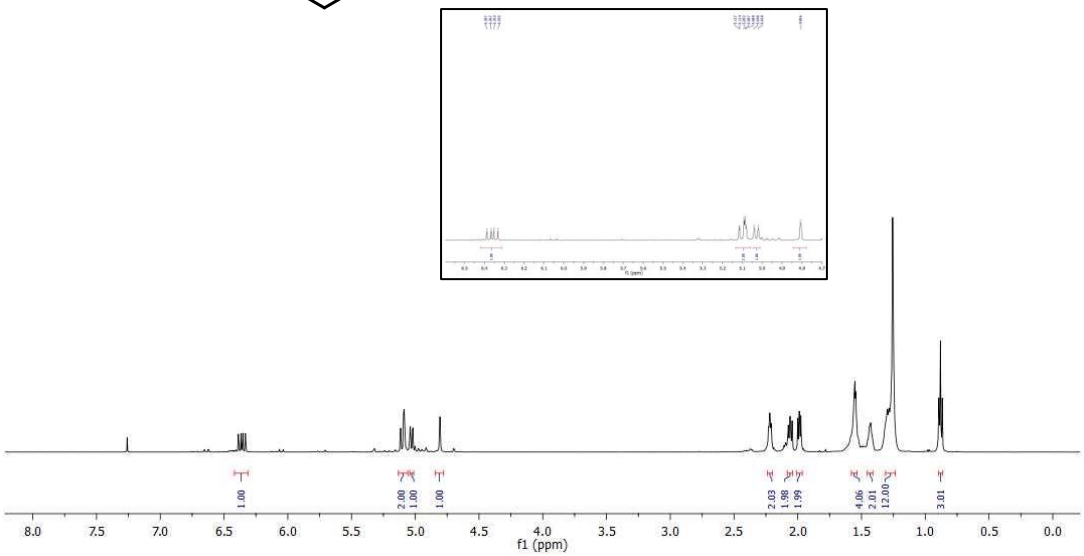

1.00
1.00
1.00
1.00
1.01
2.00
1.98
6.02
2.00
10.04
9.02
6.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

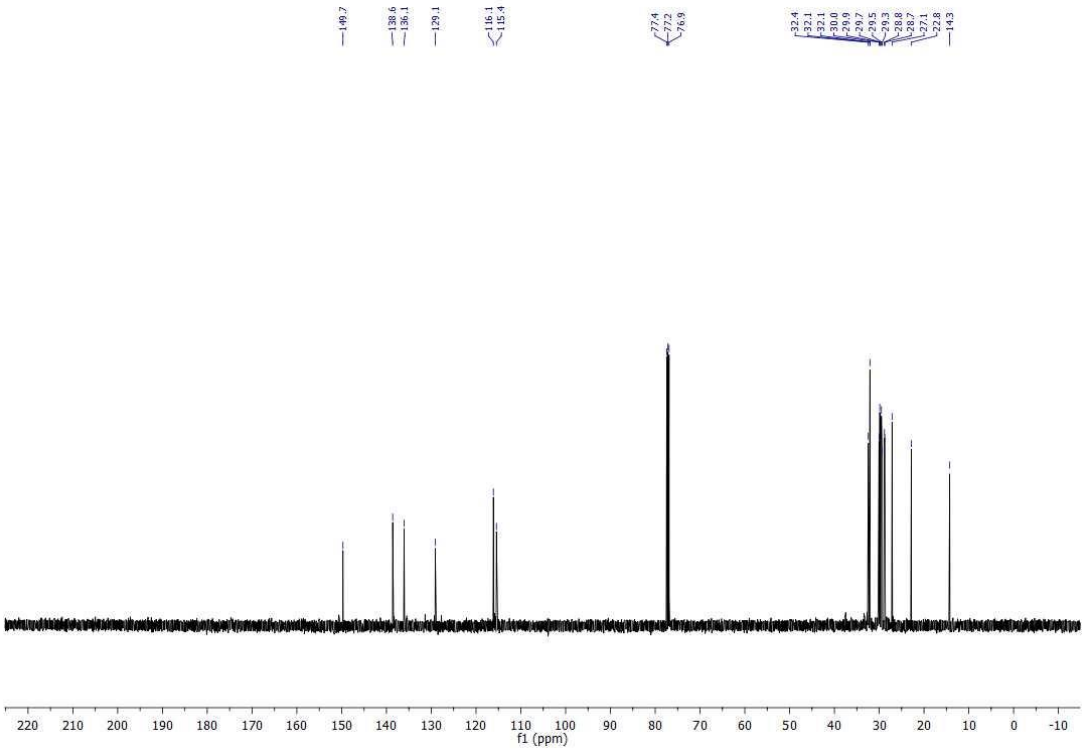

196.7
147.3
140.2
138.1
125.8
117.3
116.5
102.5
102.0
77.4
77.2
76.9
63.3
32.4
31.8
31.2
28.9
28.9
27.5
27.1
26.4
26.1
18.5
-5.1

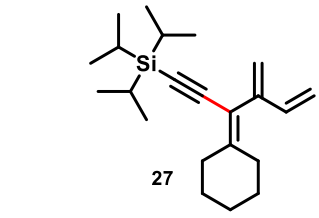

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



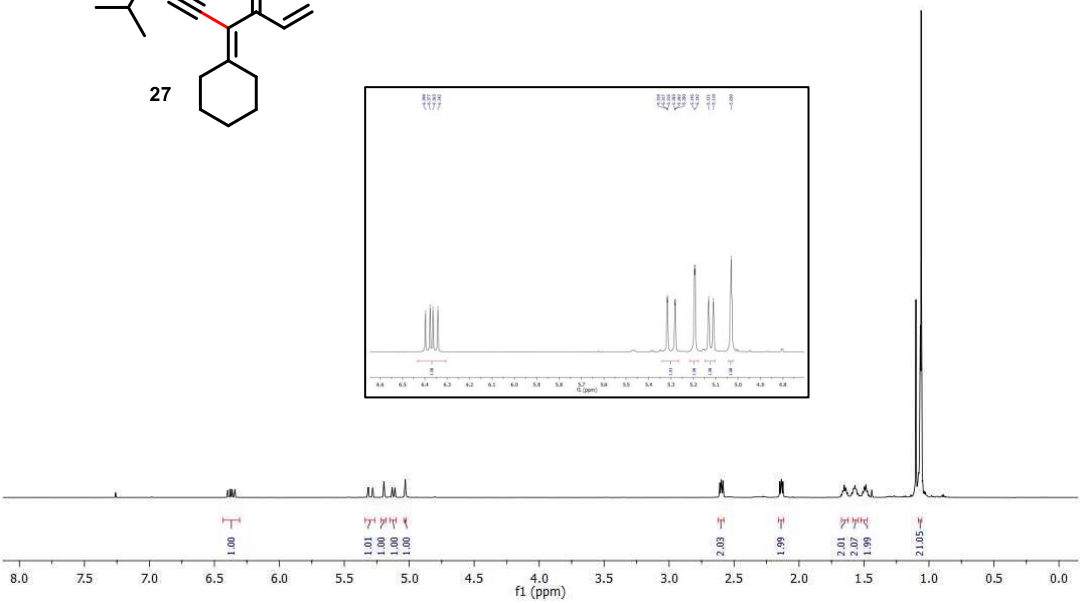
26

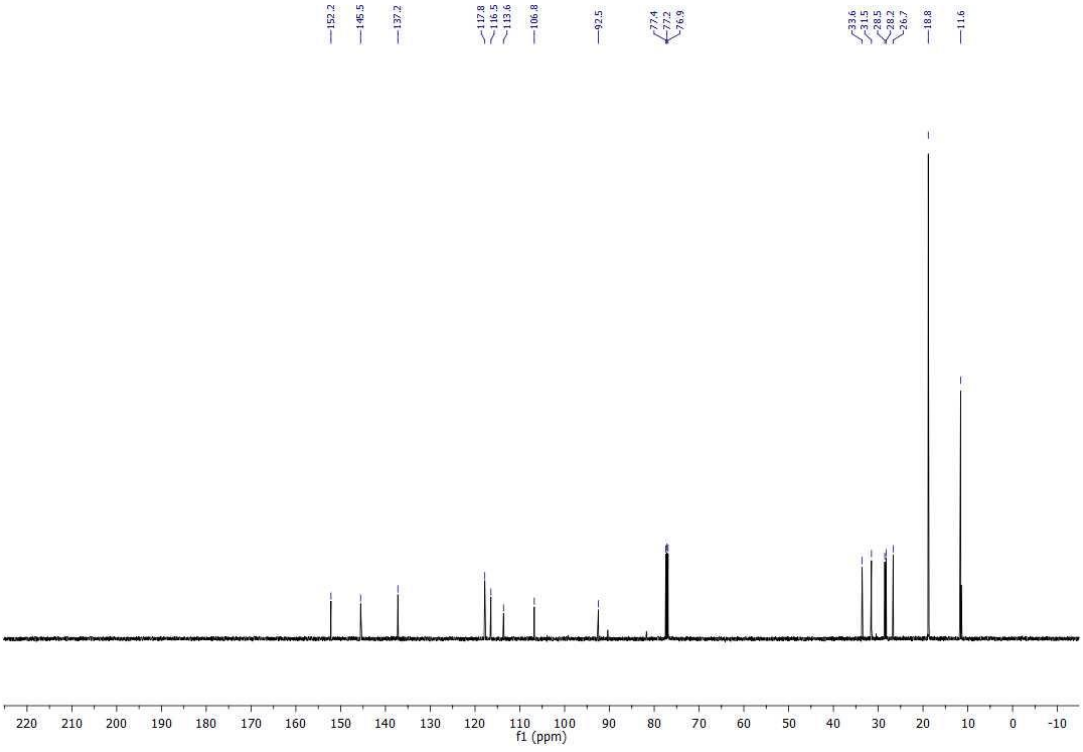

1.00
2.00
1.00
1.00
2.03
1.98
1.99
4.06
2.01
12.00
3.01
f1 (ppm)

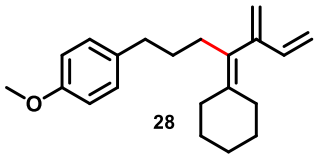

149.7
138.6
136.1
129.1
116.1
115.4
77.4
77.2
76.9
32.4
32.1
32.1
30.0
29.9
29.7
29.5
29.3
28.8
28.7
27.1
22.8
14.3
f1 (ppm)


Si

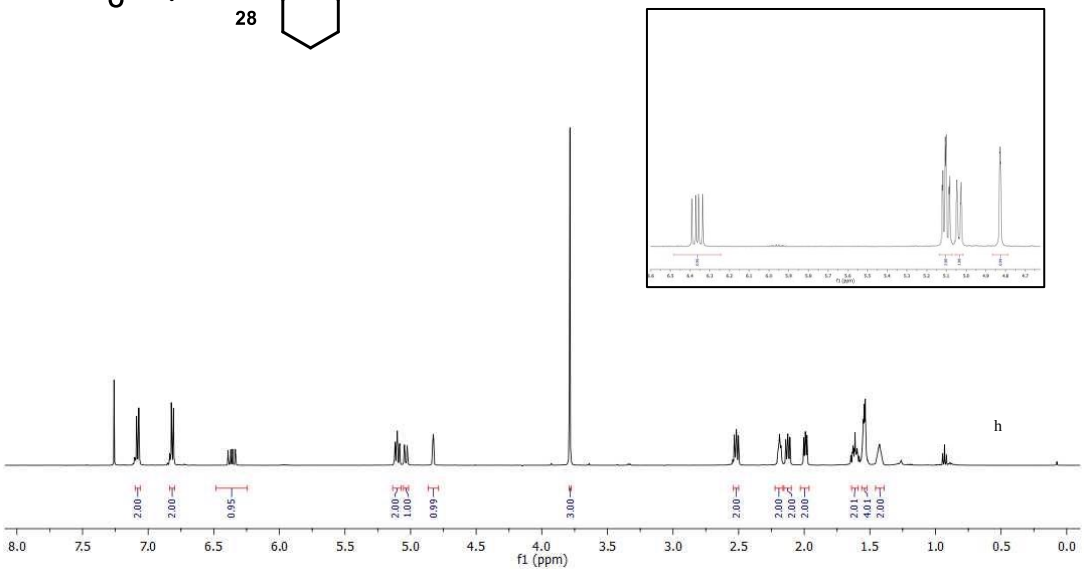
27

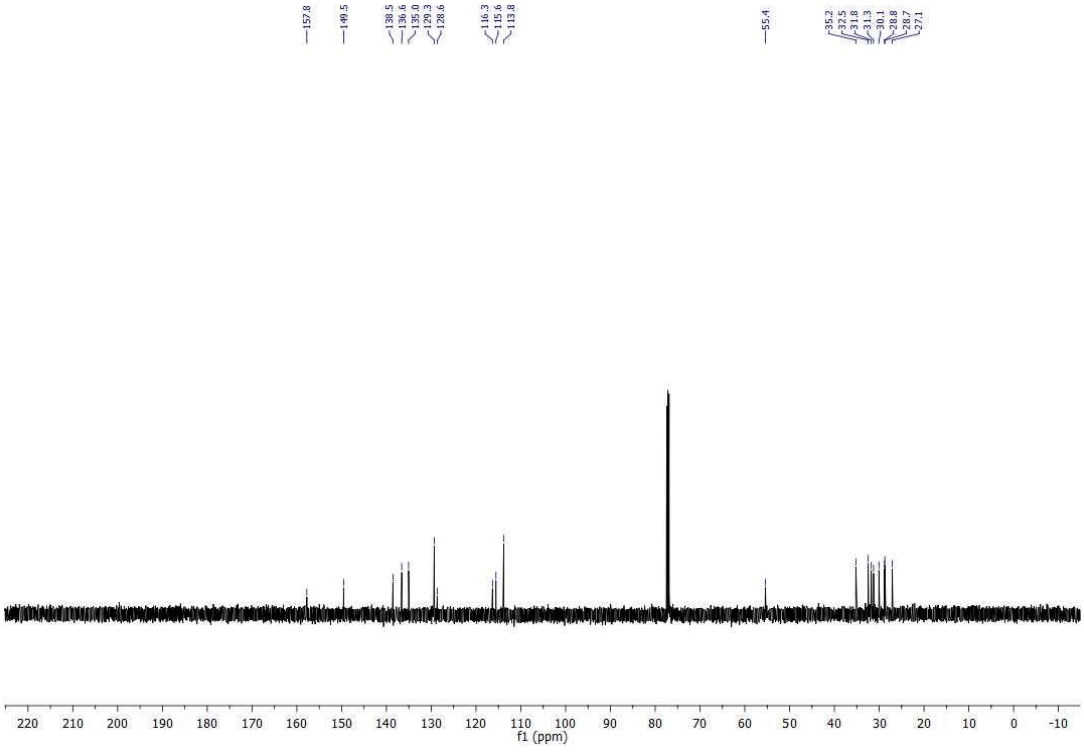

1.00
1.01
1.00
1.00
1.00
2.03
1.99
2.01
2.07
1.99
2.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

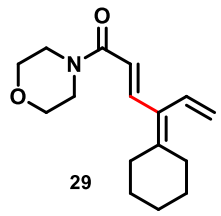

152.2
145.5
137.2
117.8
116.5
113.6
106.8
92.5
77.4
77.2
76.9
33.6
31.5
28.5
28.2
26.7
18.8
11.6
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O

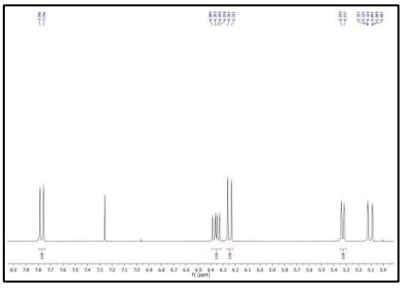
28

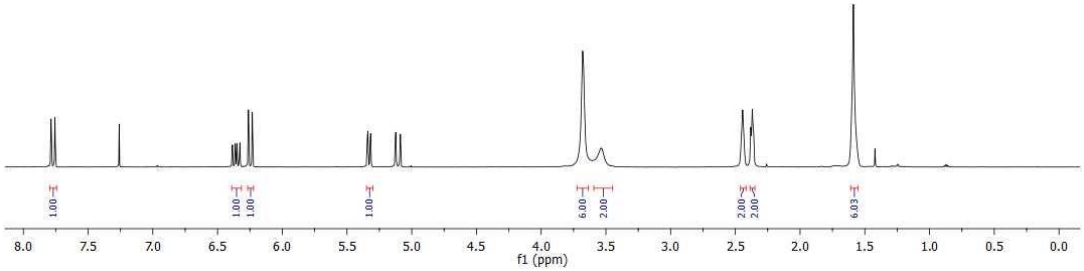

h
2.00
2.00
0.95
2.00
1.00
0.99
3.00
2.00
2.00
2.00
2.00
2.01
4.01
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


157.8
149.5
138.5
136.6
135.0
129.3
128.6
116.3
115.6
113.8
55.4
35.2
32.5
31.8
31.3
30.1
28.8
28.7
27.1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

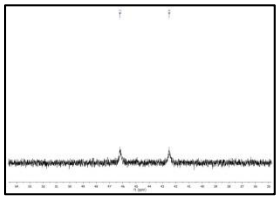

O
N
O

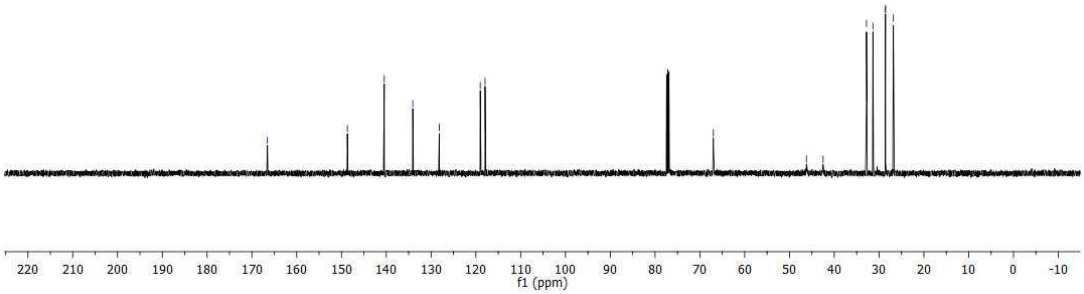
29

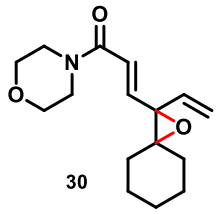



1.00
1.00
1.00
1.00
6.00
2.00
2.00
2.00
6.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

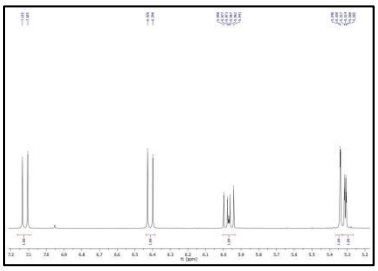

166.5
148.7
140.5
134.1
128.2
119.0
117.9
67.0
46.2
42.5
32.8
31.4
28.6
28.6
26.8

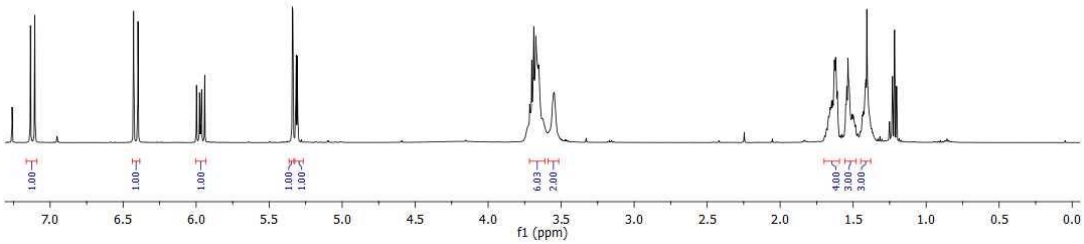



220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

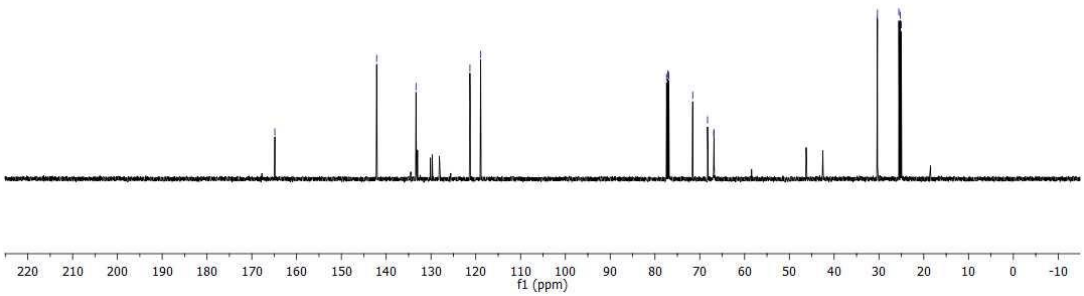

O
N
O
O

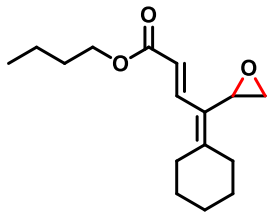
30

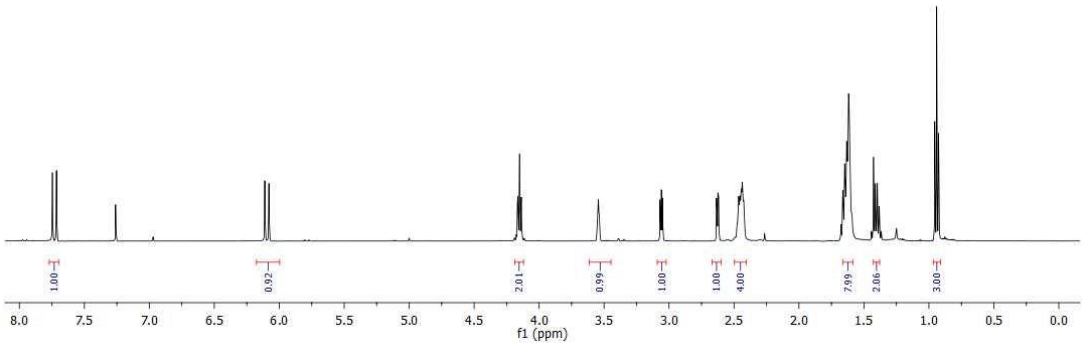


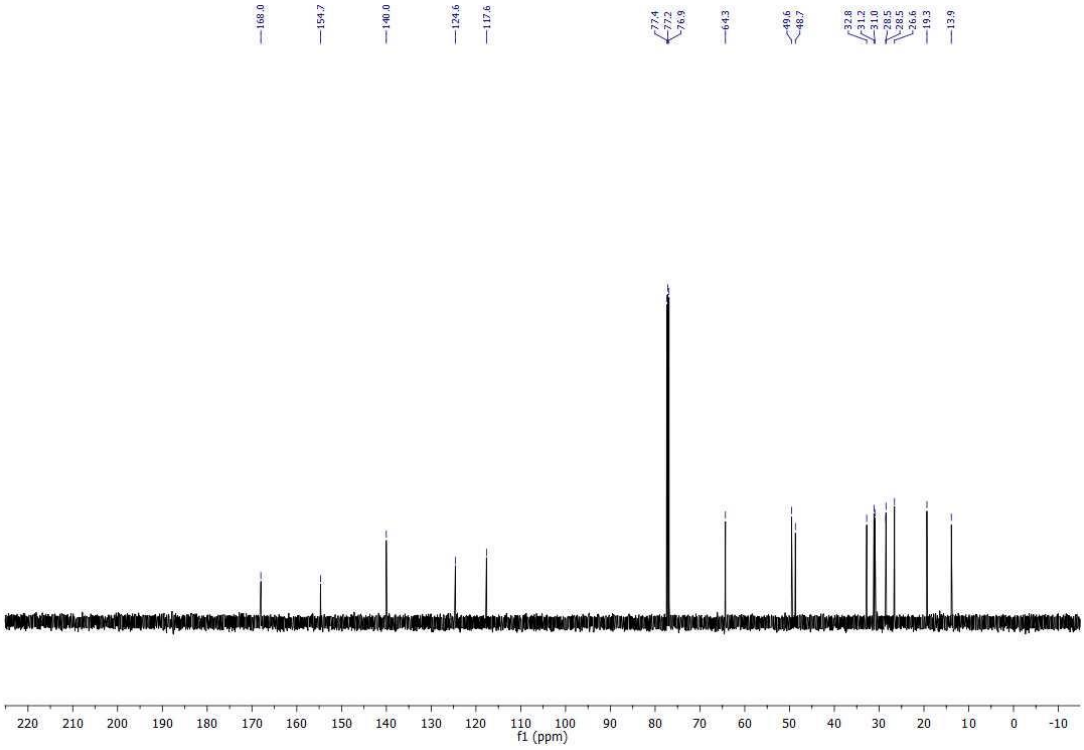

1.00
1.00
1.00
1.00
1.00
6.03
2.00
4.00
3.00
3.00
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

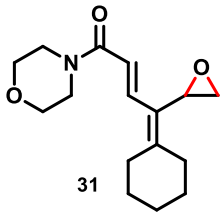

164.9
142.1
133.3
121.3
118.9
77.4
77.2
76.9
71.6
68.3
66.9
66.8
30.4
30.3
25.6
25.2
25.0


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

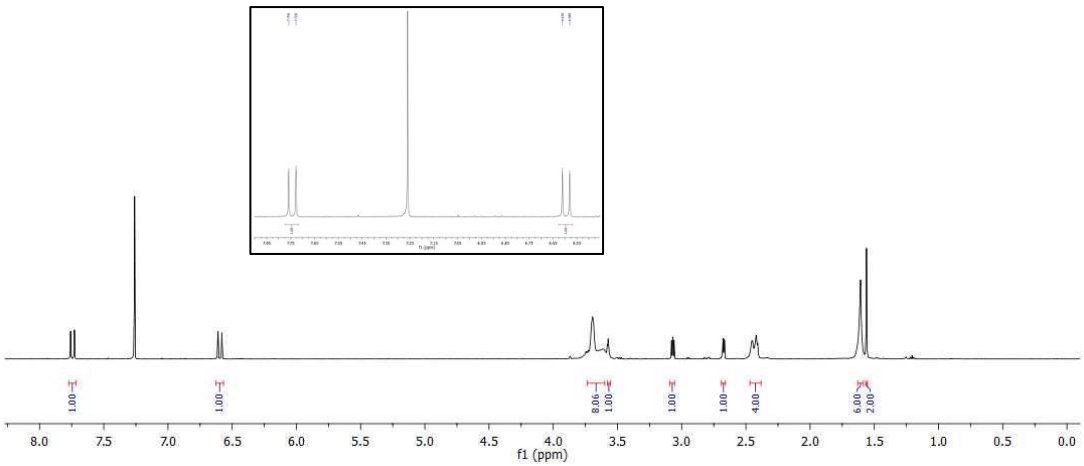


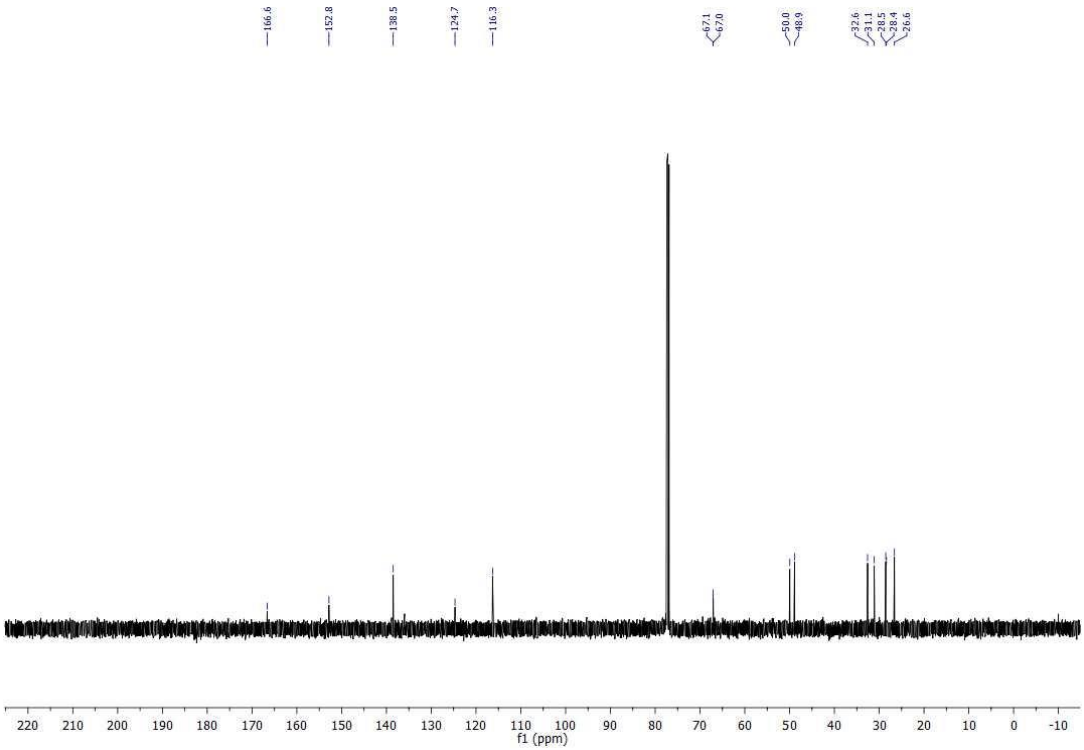

1.00
0.92
2.01
0.99
1.00
1.00
4.00
7.99
2.06
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

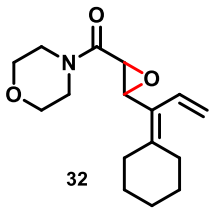

168.0
154.7
140.0
124.6
117.6
77.4
77.2
76.9
64.3
49.6
48.7
32.8
31.2
31.0
28.5
28.5
26.6
19.3
13.9
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
N
O
O

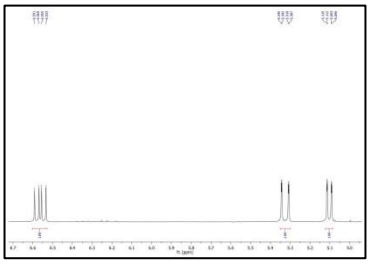
31

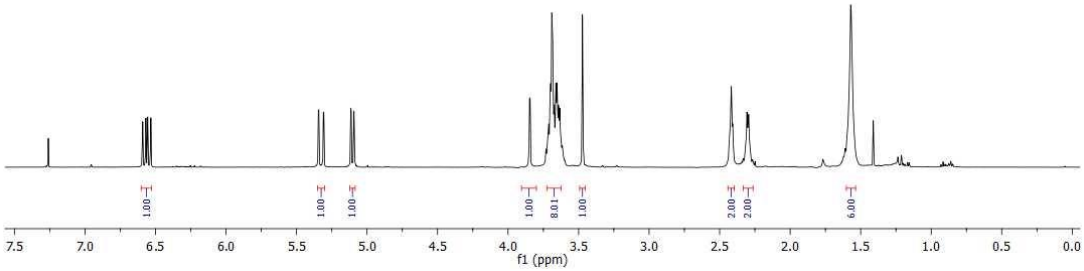

1.00
1.00
8.06
1.00
1.00
1.00
4.00
6.00
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


166.6
152.8
138.5
124.7
116.3
67.1
67.0
50.0
46.9
32.6
31.1
28.5
28.4
26.6
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

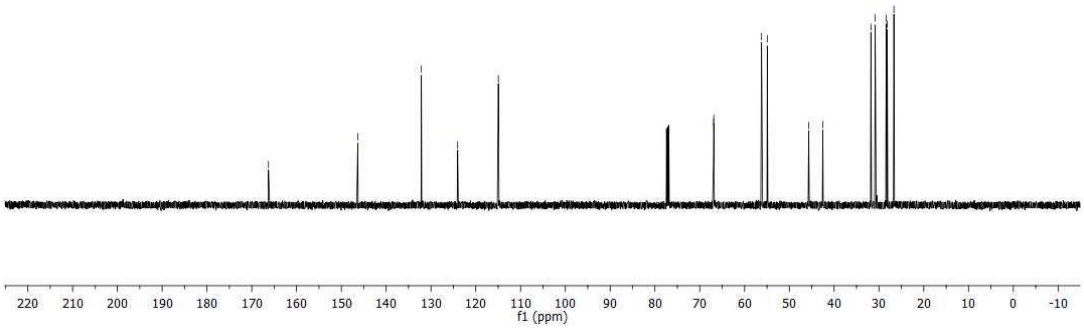

O
N
O
O

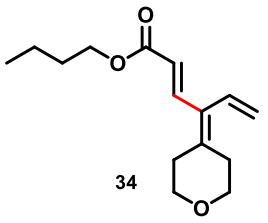
32



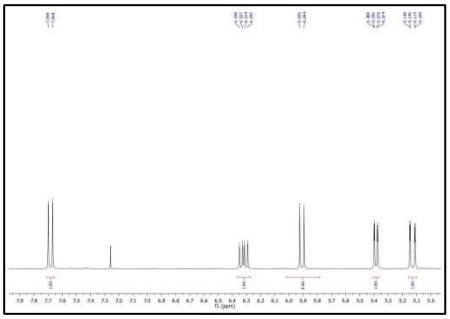

1.00
1.00
1.00
1.00
8.01
1.00
2.00
2.00
6.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

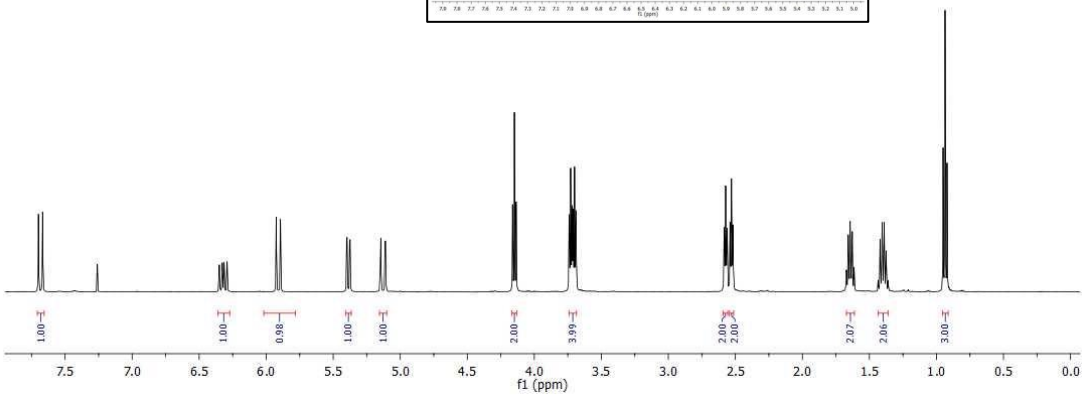

166.3
146.3
132.1
124.0
114.9
66.9
66.9
56.2
54.9
45.7
42.5
31.8
30.8
29.4
28.2
26.7


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

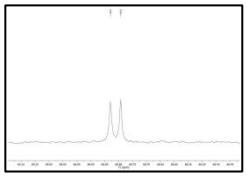

O
O
O

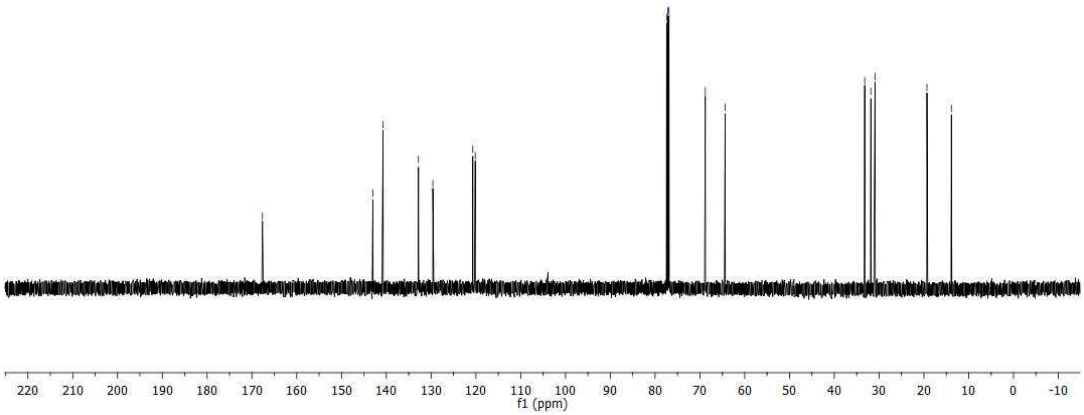
34

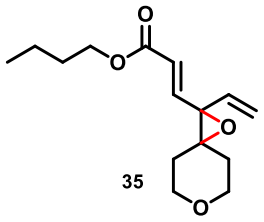


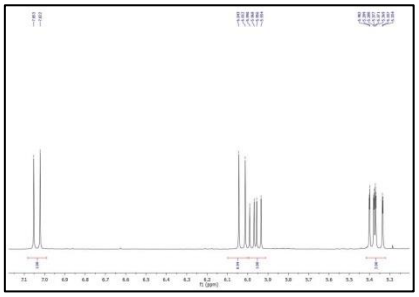

1.00
1.00
0.98
1.00
1.00
2.00
3.99
2.00
2.00
2.07
2.06
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

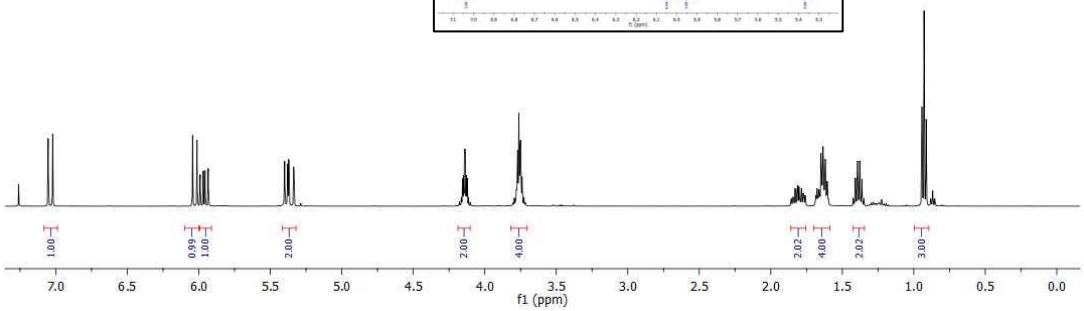

167.6
149.0
140.7
132.8
129.6
120.7
120.1
77.4
77.2
76.9
68.8
68.8
64.4
33.2
31.8
30.9
19.3
13.9



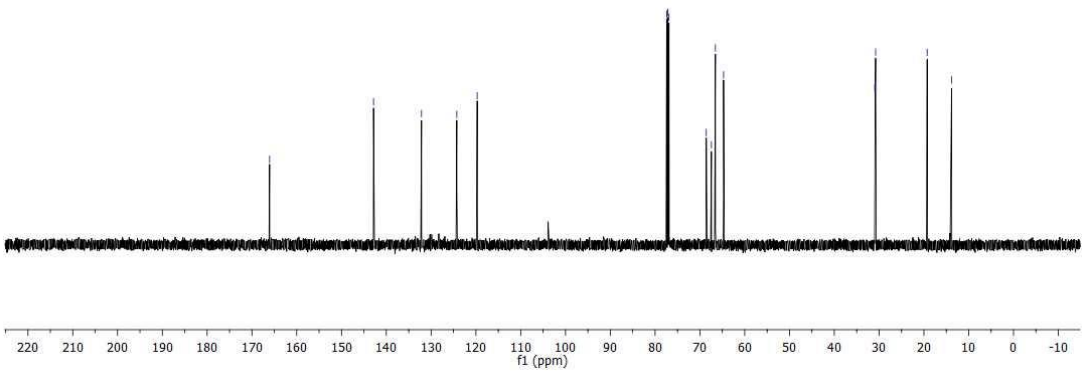

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

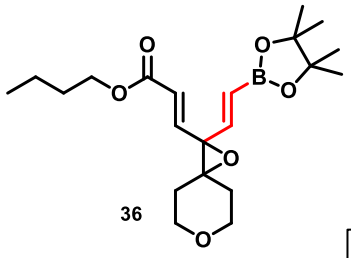

O
O
O
O
35



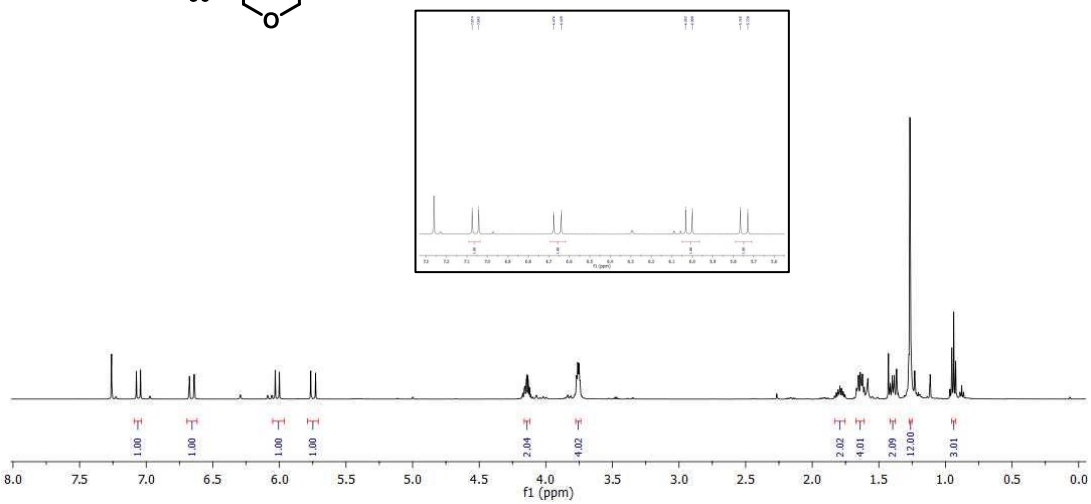

1.00
0.99
1.00
2.00
2.00
4.00
2.02
4.00
2.02
3.00
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

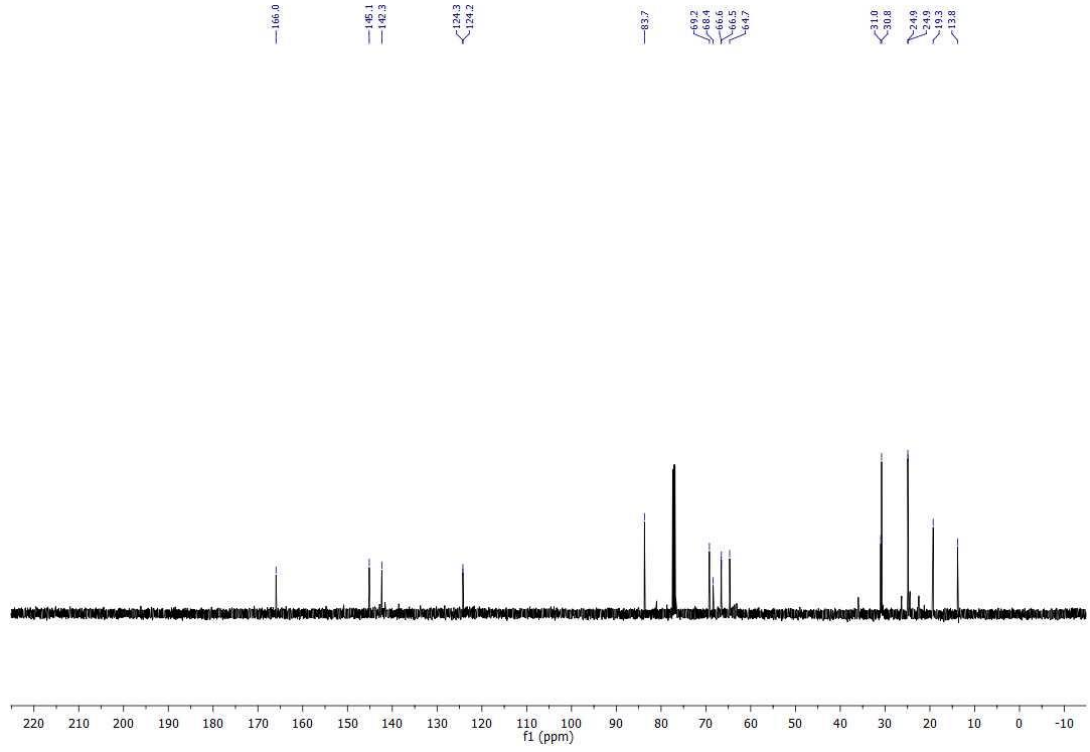

166.1
142.9
132.1
124.3
119.7
77.4
77.2
76.9
68.6
67.4
66.5
66.5
64.7
31.0
30.9
30.8
19.3
13.8

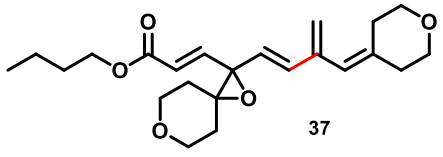

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
B
O
O
O
O

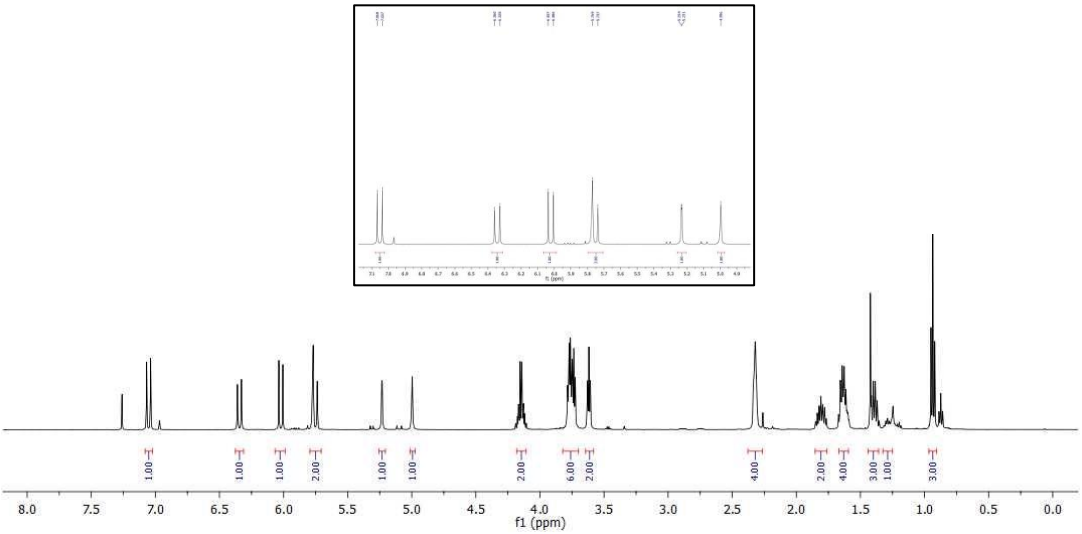
36

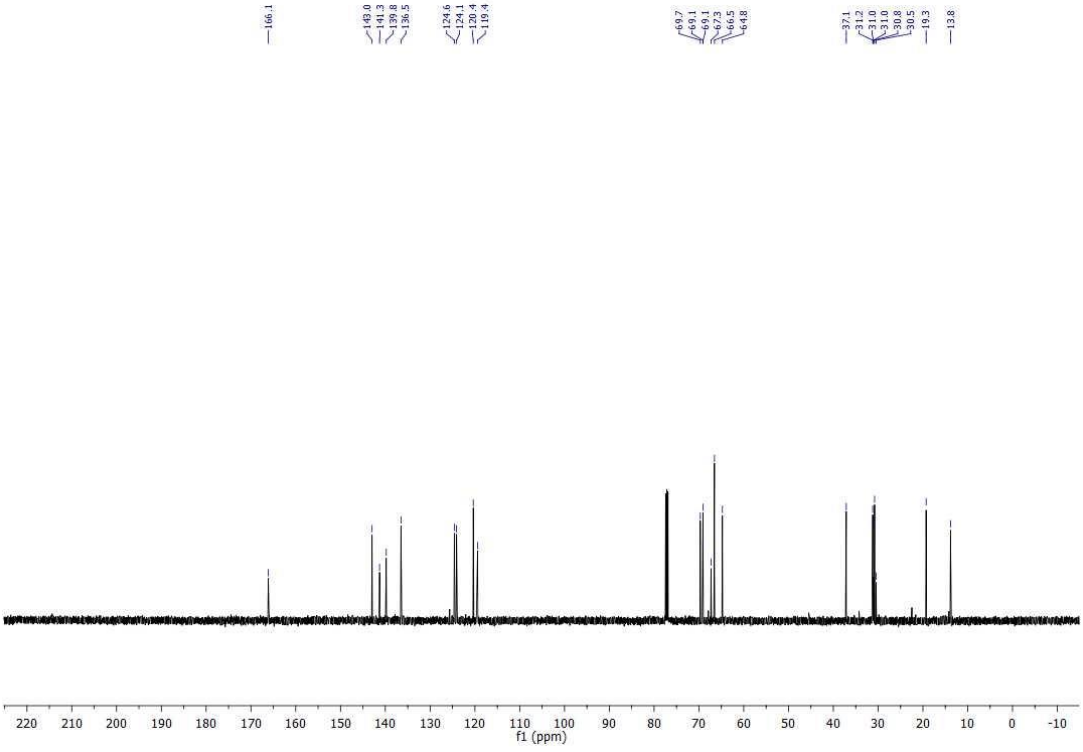

1.00
1.00
1.00
1.00
2.04
4.02
2.02
4.01
2.09
12.00
3.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

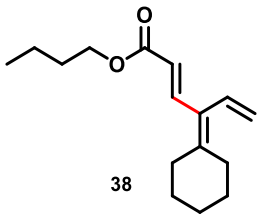

166.0
145.1
142.3
124.3
124.2
83.7
69.2
68.4
66.6
66.5
64.7
31.0
30.8
24.9
24.9
19.3
13.8
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



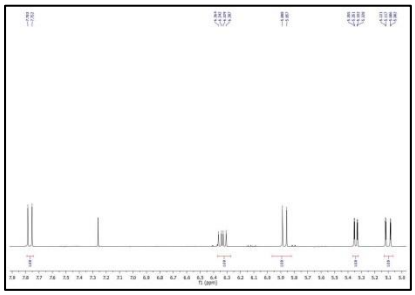
37

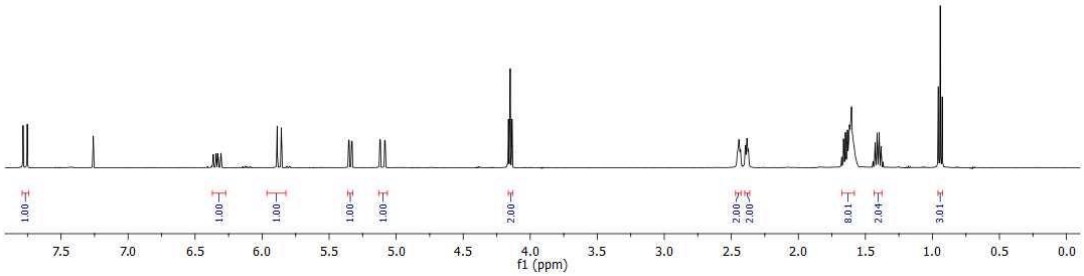

1.00
1.00
1.00
2.00
1.00
1.00
2.00
6.00
2.00
4.00
2.00
4.00
3.00
1.00
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


166.1
145.0
141.3
139.8
136.5
124.6
124.1
120.4
119.4
69.7
69.1
69.1
67.3
66.5
64.8
37.1
31.2
31.0
31.0
30.8
30.5
19.3
13.8
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

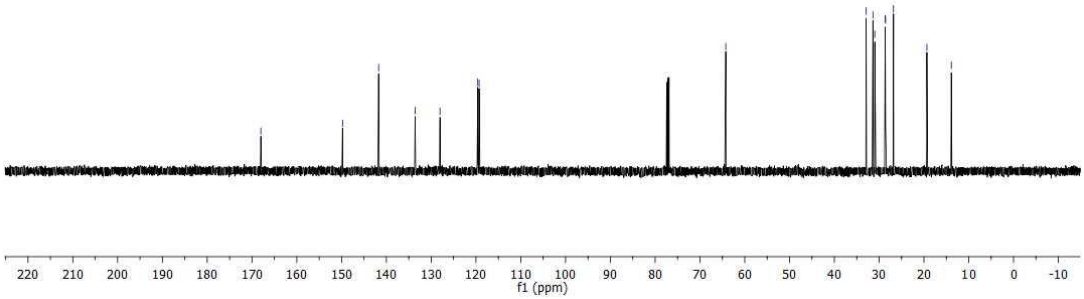

O
O

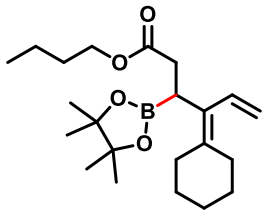
38



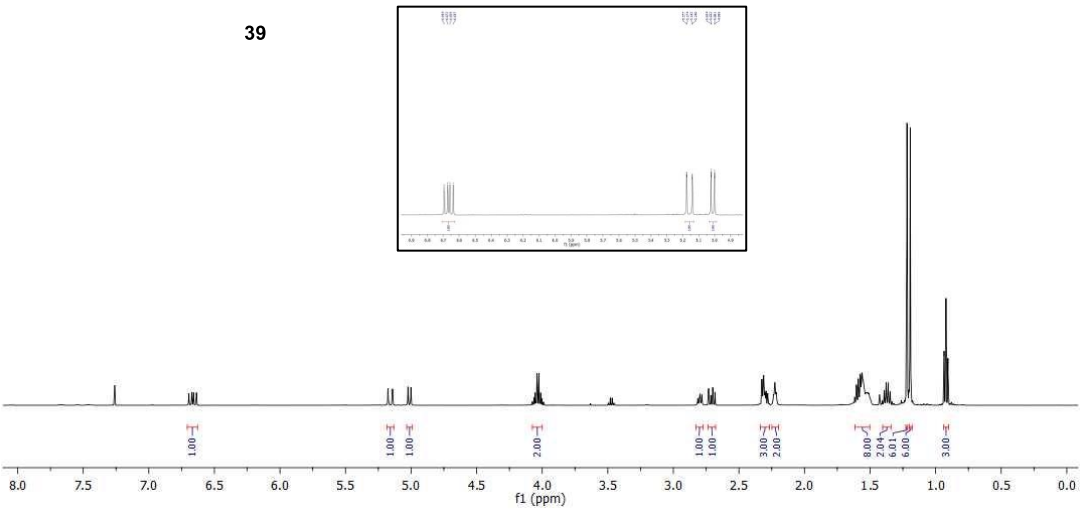

1.00
1.00
1.00
1.00
1.00
2.00
2.00
2.00
8.01
2.04
3.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

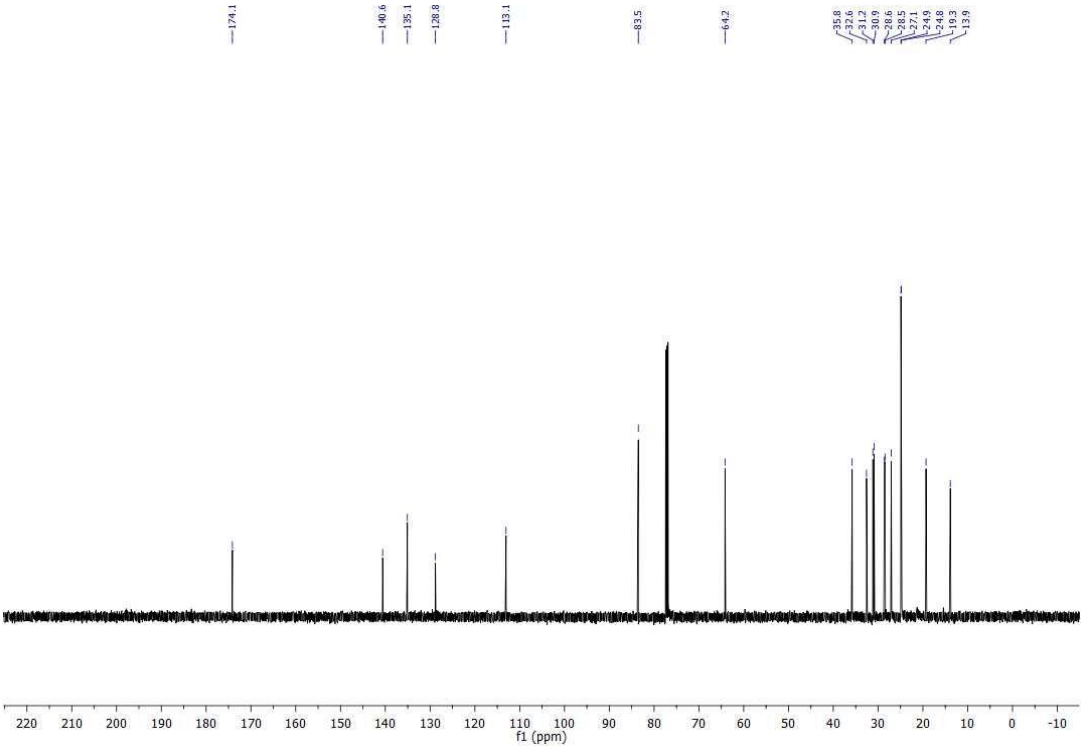

168.0
149.8
141.7
133.6
128.0
119.6
119.3
64.2
32.9
31.4
31.0
28.6
28.6
26.8
19.3
13.9

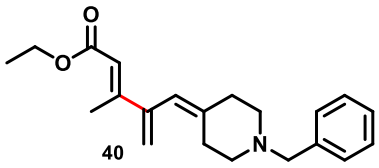

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



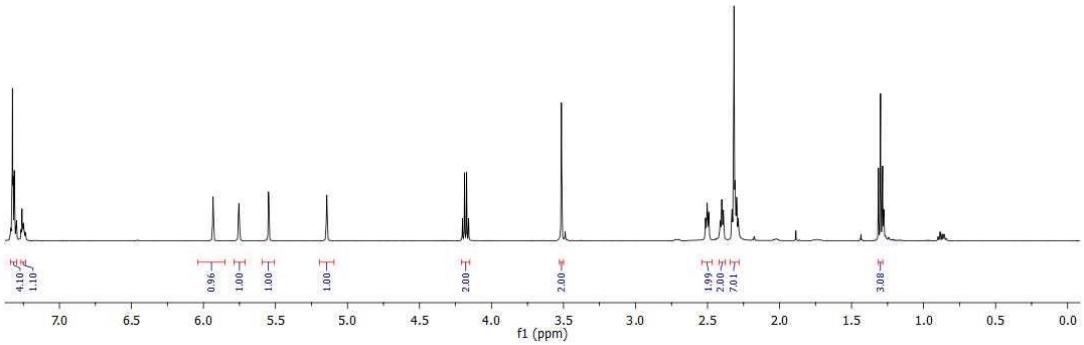
39


1.00
1.00
1.00
2.00
1.00
1.00
3.00
2.00
8.00
2.04
6.01
6.00
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

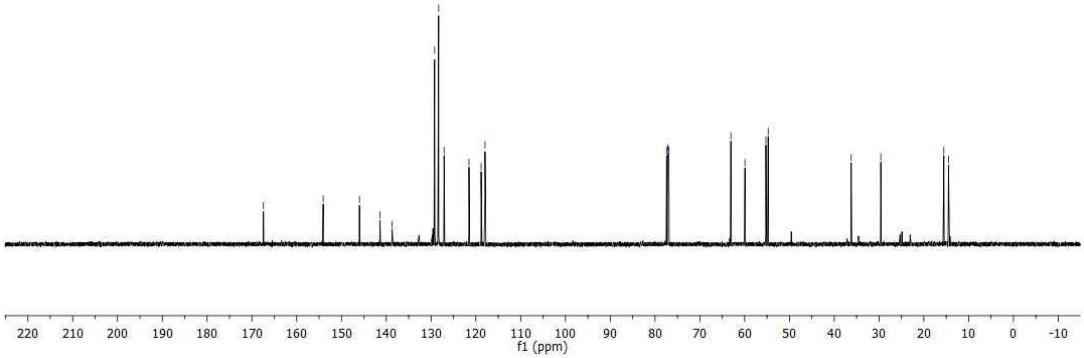

174.1
140.6
135.1
128.8
113.1
83.5
64.2
35.8
32.6
31.2
30.9
28.6
28.5
27.1
24.9
24.8
19.3
13.9
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

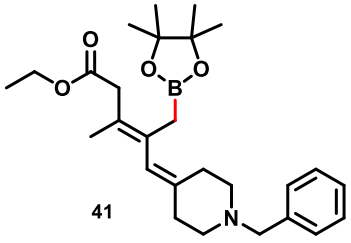

O
O
N

40

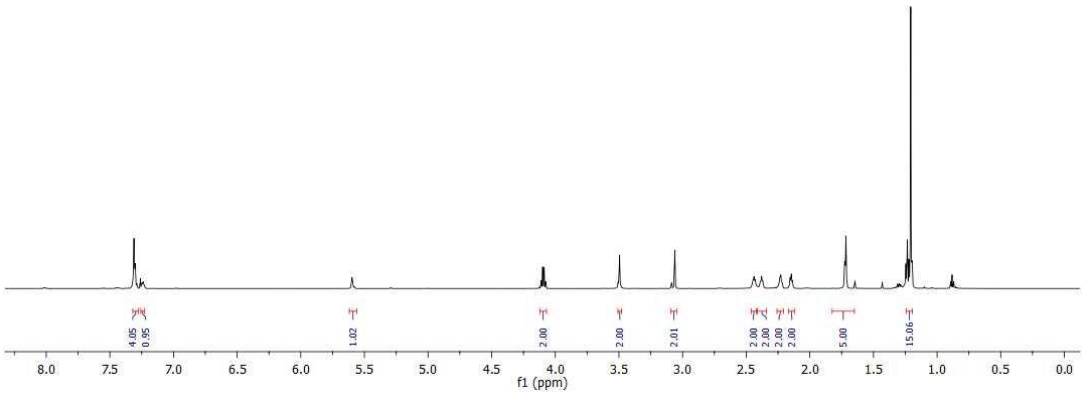

4.10
1.10
0.96
1.00
1.00
1.00
2.00
2.00
1.99
2.00
7.01
3.08
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


167.4
154.1
146.0
141.4
138.7
129.2
128.3
127.1
121.5
118.8
117.9
77.4
77.2
76.9
63.1
59.6
55.3
54.8
36.2
29.6
15.5
14.5

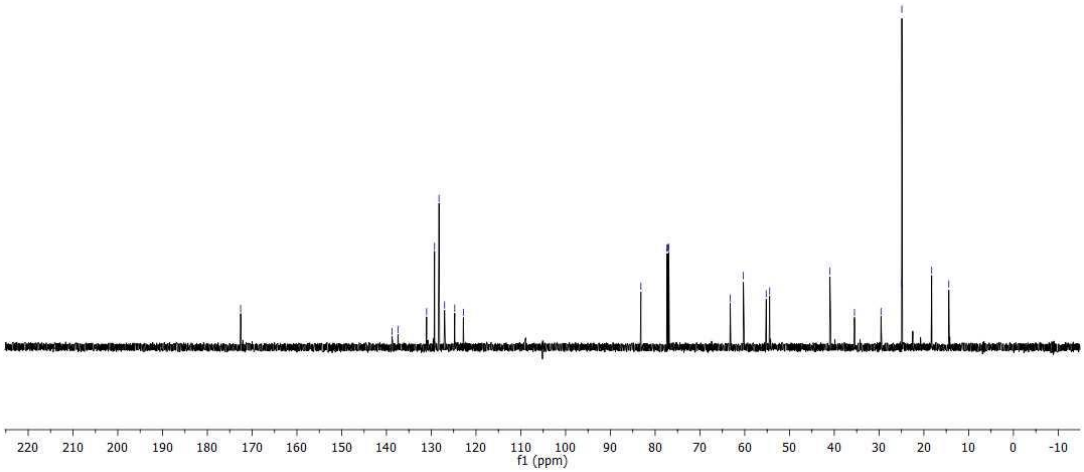

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

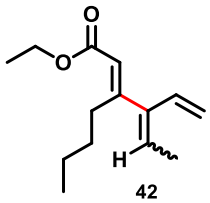

O
O
O
B
O
N

41

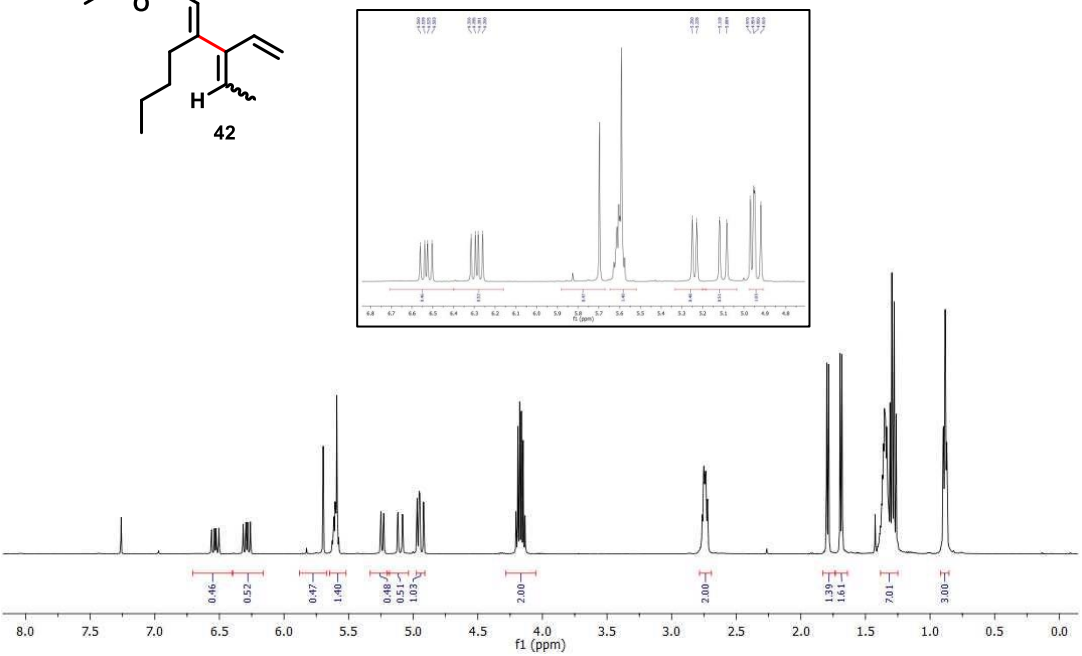

4.05
0.95
1.02
2.00
2.00
2.01
2.00
2.00
2.00
5.00
15.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


172.6
138.8
137.4
131.0
129.3
128.3
127.0
124.8
122.8
83.2
77.4
77.2
76.9
63.2
60.3
55.2
54.4
41.0
35.5
29.6
24.9
24.9
18.2
14.4


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
H

42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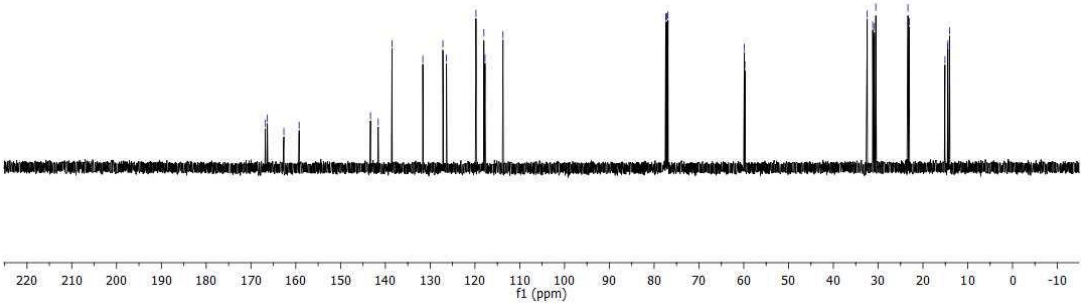
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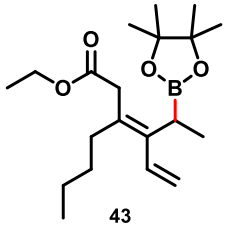
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O
B
O

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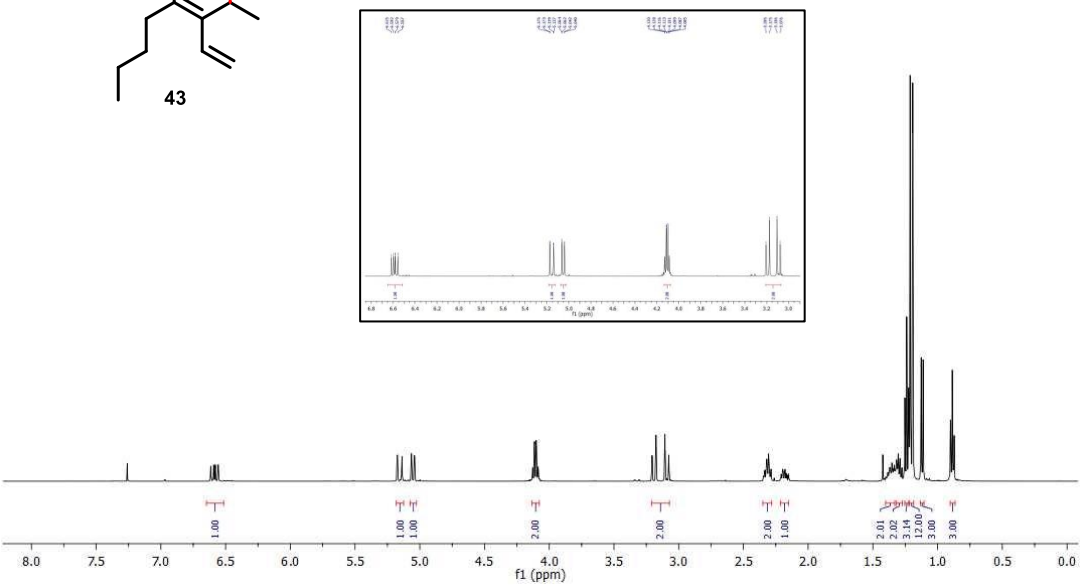
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6.5
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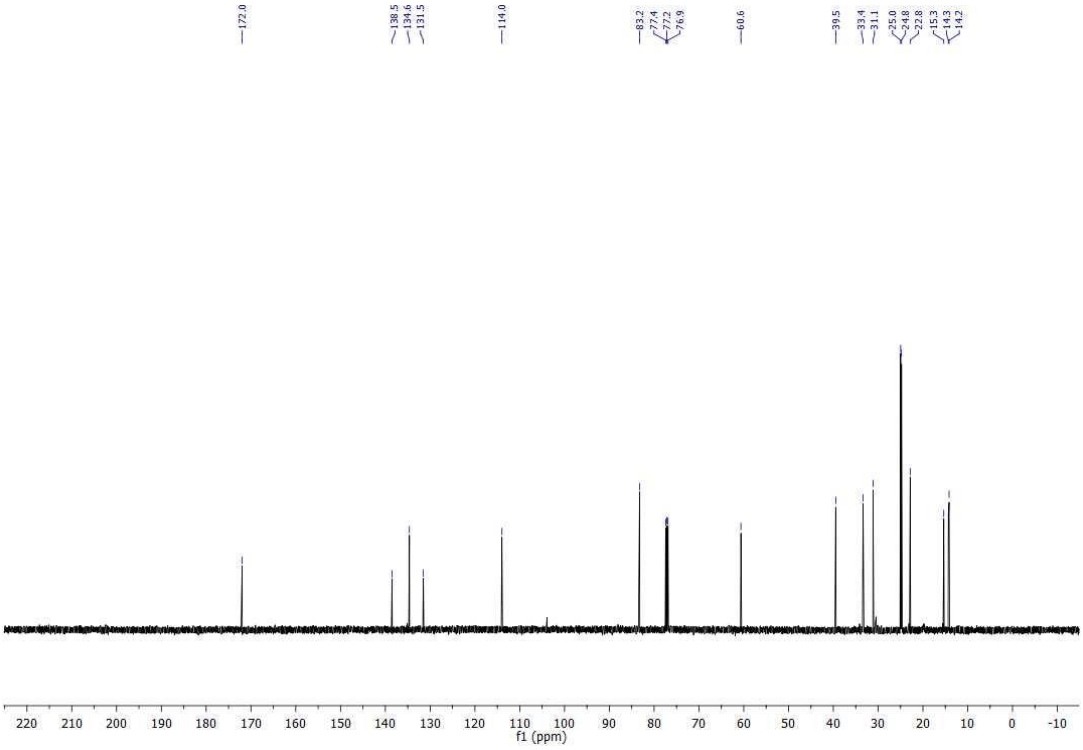
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25.0
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22.8
15.3
14.3
14.2
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190
180
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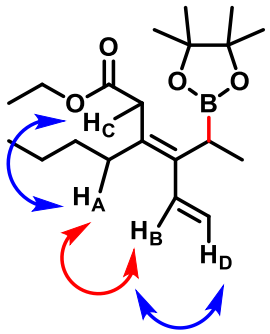
f1 (ppm)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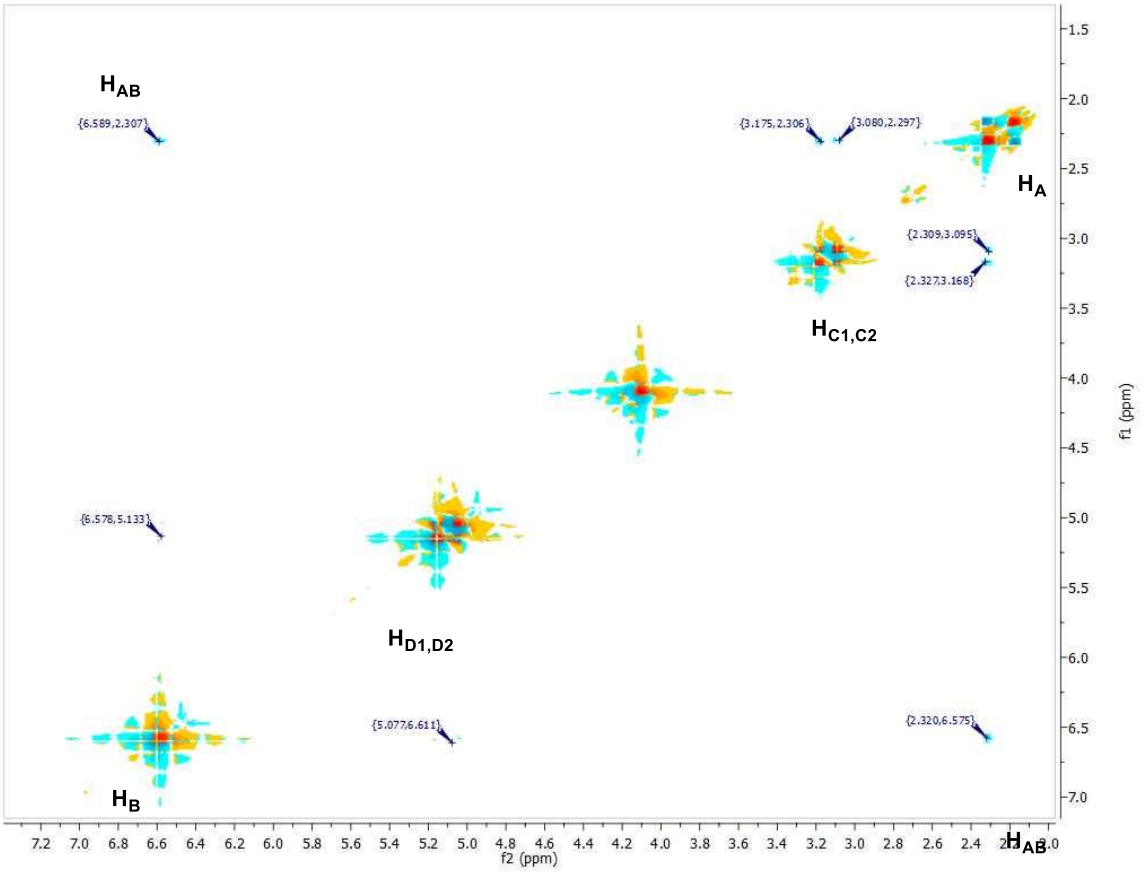
O
H_C
H_A
H_B
H_D

43

2D : NOESY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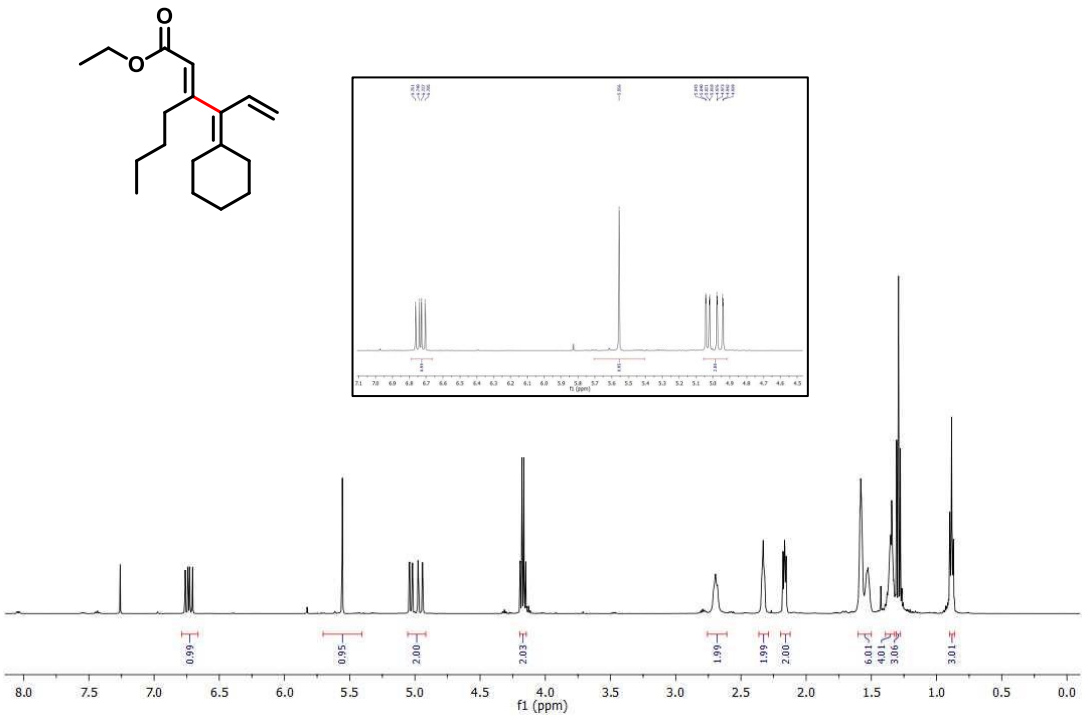
H_AB
f2 (ppm)
f1 (ppm)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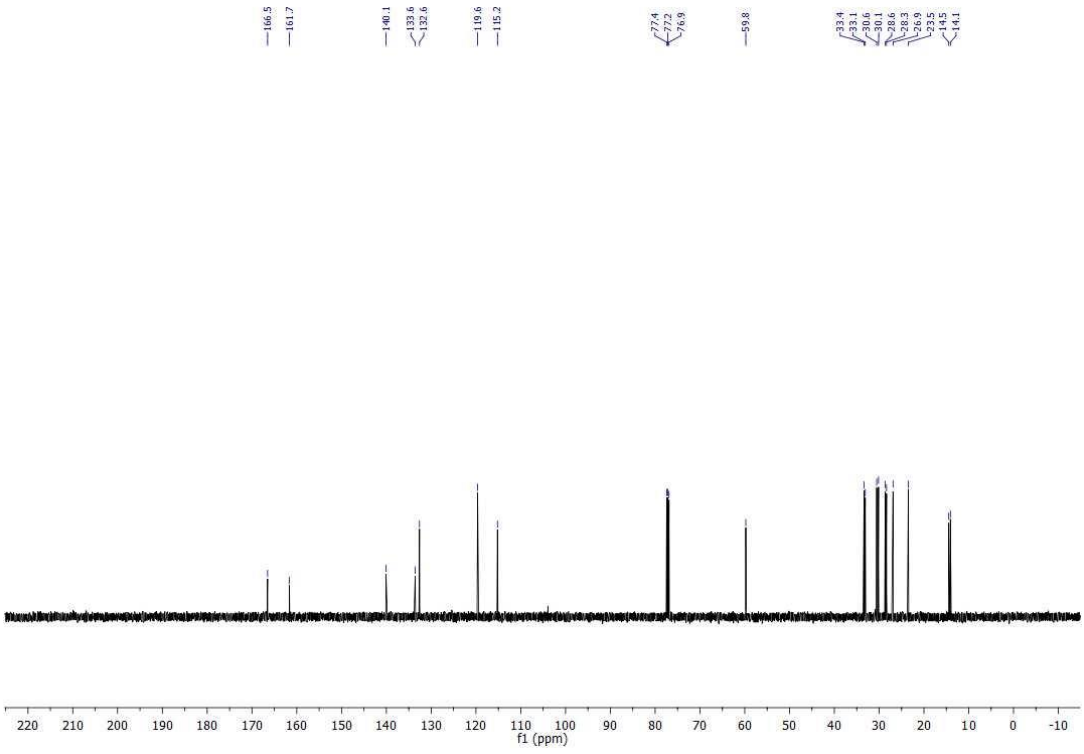
f1 (ppm)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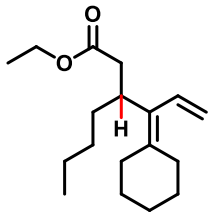
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O
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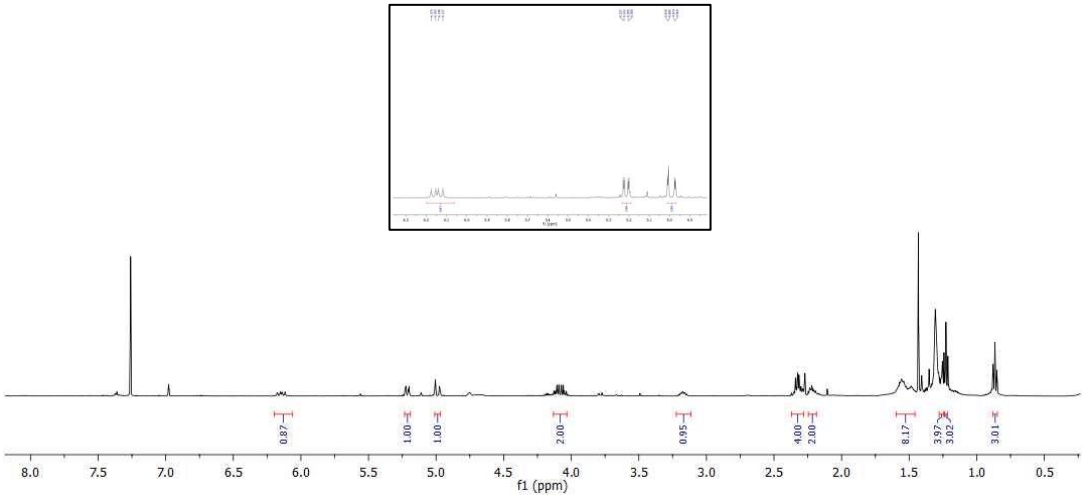
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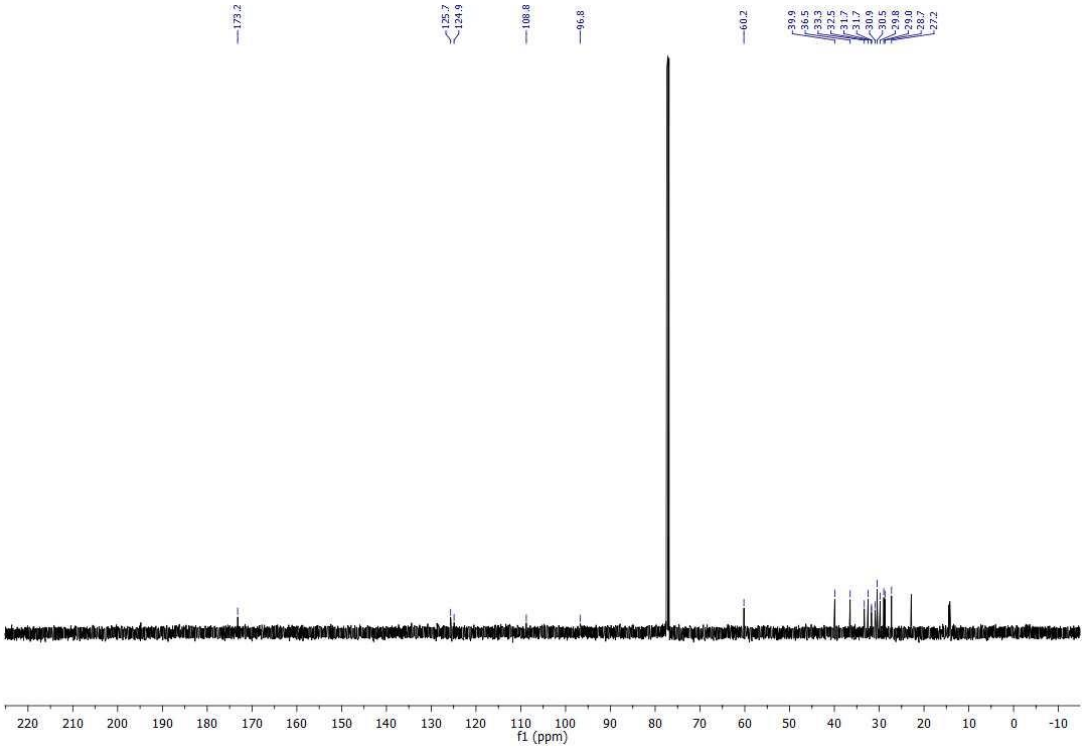
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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96.8
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32.5
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30.9
30.5
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28.7
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-10
f1 (ppm)

III. Copper-Catalyzed Oxidative Cleavage of Electron-Rich Olefins in Water at Room Temperature

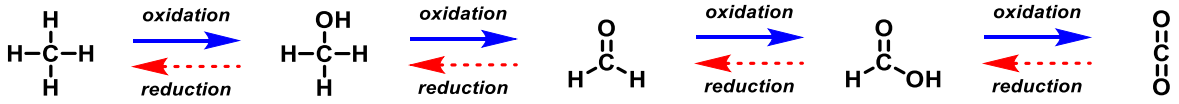
"¿…Que onda…?"

-Pedro J. Trejo-Soto

3.1. Introduction and Background

Oxidation reactions represent an important and fundamental area of organic chemistry. Coupled with reduction reactions, the term 'redox' is born; a rudimentary concept familiar to all chemists and chemical disciplines. An elementary example of varying oxidation-states for a single carbon center is illustrated in Figure 1. Furthermore, oxidation is arguably the most commonly observed and utilized transformation in Nature, and within all living things (perhaps closely rivaled with that of point-methylation; when viewed in terms of importance and repercussions). Its power in synthesis, as evidenced by the many classically known 'name reactions,' and the continued development of new oxidation processes, is strong justification for its worth to chemists and value in chemistry.

Figure 1. Generalization of a Single Carbon's Oxidation States

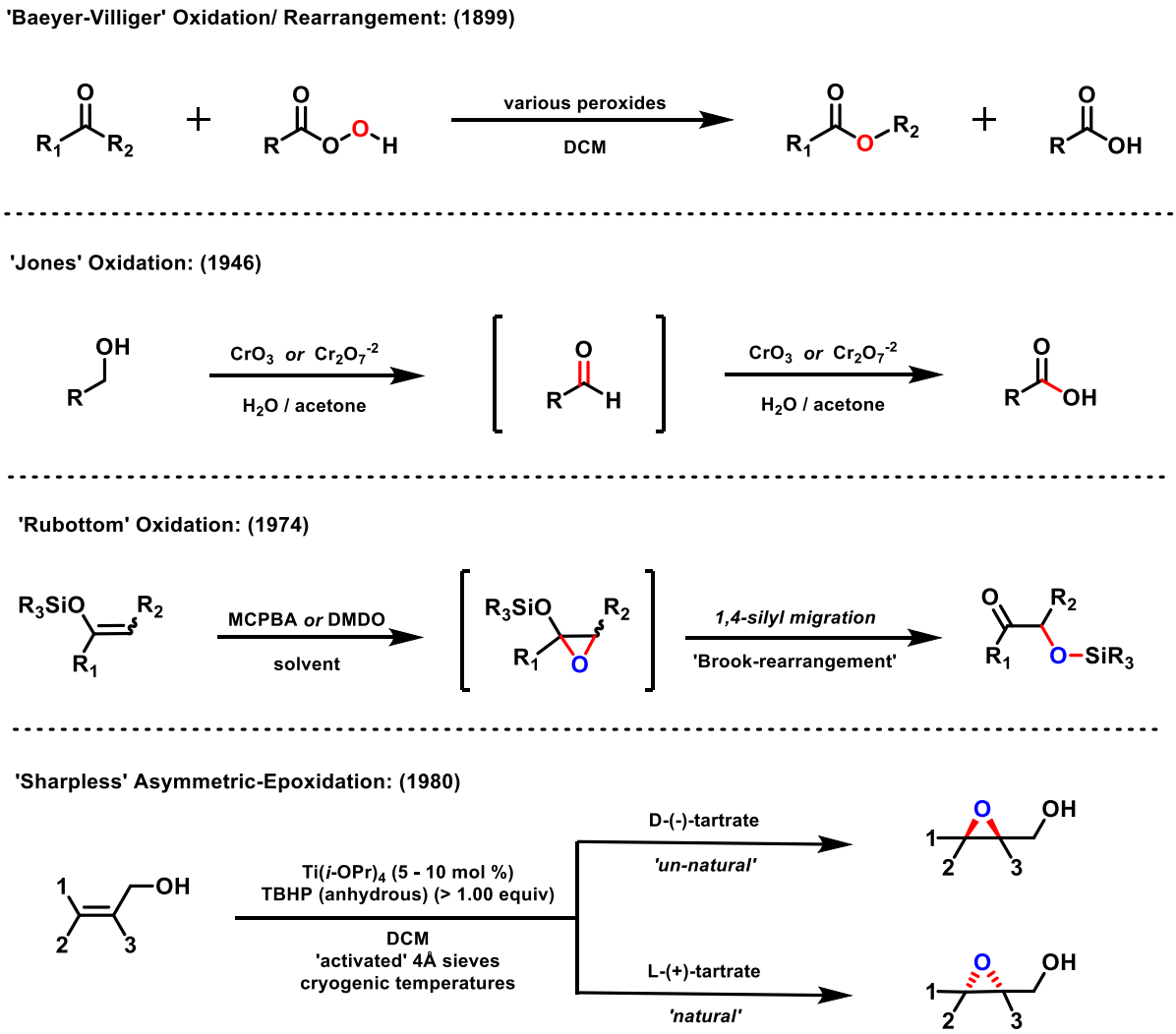


Of the many 'oxidative name reactions' known a few of the more popular and widely utilized transformations are illustrated in Figure 2. Thus, as early as 1899 the conversion of ketones (cyclic or acyclic) to their corresponding ester was developed by the pioneers Baeyer and Villiger.[1] This process was achieved by the activity of the stoichiometric oxidant MCPBA,

and its mechanism deconvoluted in 1953 by Doering and Dorfman.[1c] Oxidation of alcohols (*e.g.,* primary alcohols) with the highly reactive and toxic reagent chromic acid affords, initially, the first oxidation-level product aldehyde. With increased equivalents of H_2CrO_4, water, and time, the initial aldehyde is then converted to the secondary oxidation product carboxylic acid; this reaction is referred to as the 'Jones-oxidation,' discovered by Jones in 1946.[2a] More recently this highly acidic reagent has been replaced with pyridinium chlorochromate (PCC) by Corey in 1975;[2b] which was the product of continual advancement; first by Sarret (1953),[2c] and then by Collins (1968; Collins-reagent),[2d] and lastly by Corey again in 1979 to afford 'neutral' pyridinium dichromate (PDC).[2e] The 'Rubottom-oxidation' (1974) is a noteworthy reaction to mention because of the similarity of educts (protected enol ethers) and oxidants (organic peroxides) utilized when compared to our systems (*vide infra*) to afford different 'net' adducts; in this case α-hydroxy ketones.[3] The differences in reaction outcome is most likely an effect of organometallic catalysis; as in our case we employ a copper (Cu) catalyst, whereas the 'Rubottom' is transition metal-free. The conversion of primary alcohols to aldehyde, or secondary alcohols to ketones, through an *in situ* directing-group/elimination process has been an enduring reaction in methodology research. This important transformation has been improved upon incrementally over the 20th century and continues to be further developed to this day.[4a] In this regard the most notable progressions include: The 'Oppenauer' (1937);[4b-c] the 'Corey-Kim' (1972);[4d] the 'Swern' (1976, 1978); [4e-i] the 'Dess-Martin' (1983); [4j-l] and the 'Ley-oxidation' (1985). [4m-q] Another, very useful, directed oxidation reaction (of allylic alcohols) is the 'Sharpless asymmetric-epoxidation,' where the combination of a 'pre-aged' titanium-(+ or -) tartrate-based catalyst scaffold, anhydrous (activated sieves) cryogenic (-24 ^{o}C or below) conditions, and TBHP (*tert*-butyl hydroperoxide) organize themselves in

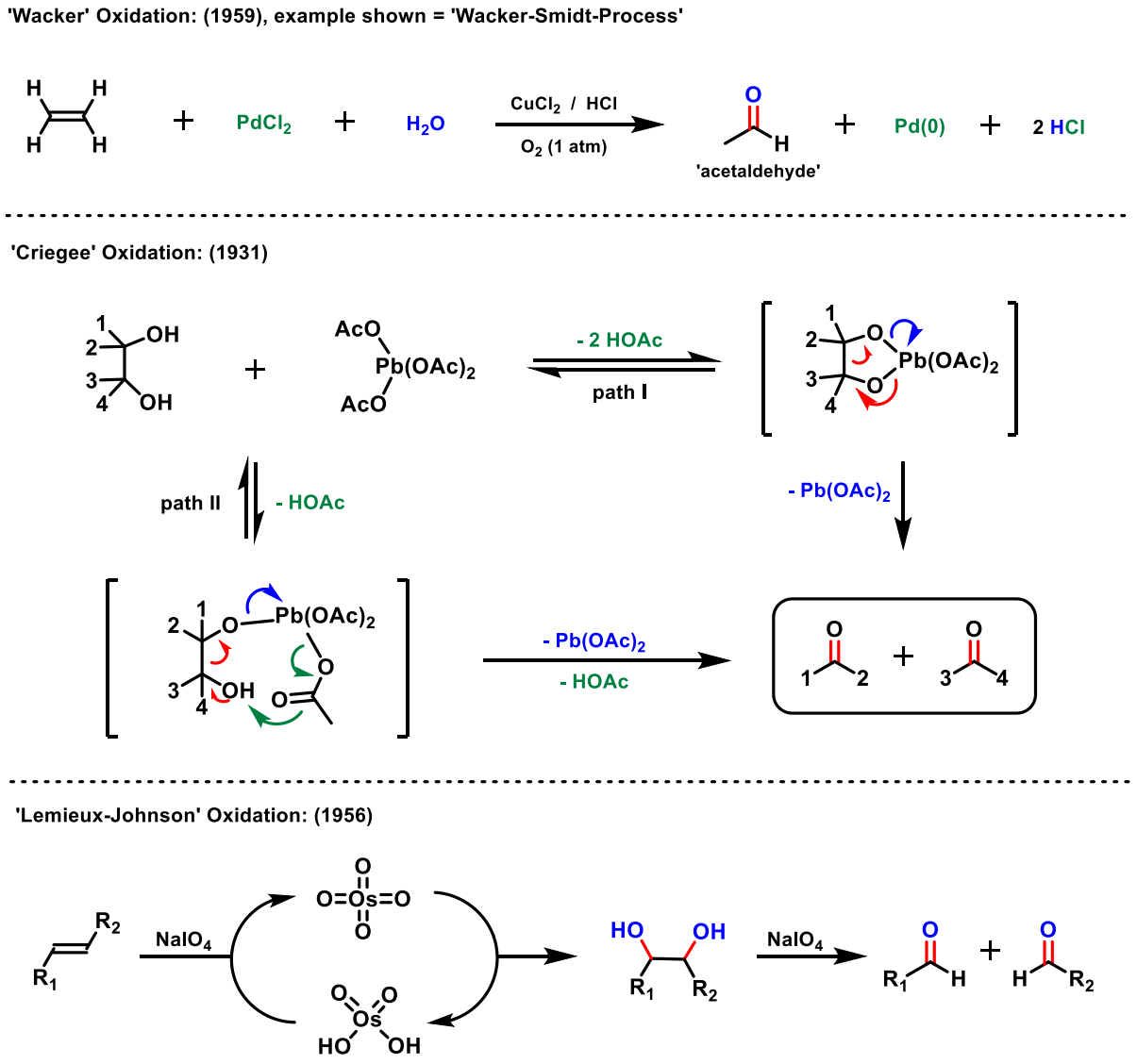
such a way that upon introduction of the allylic alcohol substrate, a detailed 'catalytic-pocket' arises. The result of this is exceptional control of olefin selectivity (only allylic alcohols react) as well as control of facial selectivity, with enantiomeric excesses (% ee's) uniformly being very high.

Figure 2. Historical Oxidation Reactions in Organic Synthesis



However, and more specifically within oxidation reactions are those transformations that convert an olefin into a carbonyl functionality, as represented in Figure 3. Reactions that fall into this category include, but are not necessarily limited to, the following: The 'Wacker-Schmidt' process, an advance of Phillips' work in 1894,[5a] which led to the early industrial oxidation of ethylene gas into acetaldehyde. Of further note is that it was adopted early on as one of the first available methods for detecting, qualitatively, the presence of an olefin in a reaction mixture *via* the observation of precipitation in the form of palladium(0). The 'Wacker-oxidation' (1959) utilized the advantages of copper additives thereby allowing for the overall process to become catalytic in palladium (Figure 3, top).[5b-e] The 'Criegee-oxidation' (1931) (not to be mistaken with the 'Criegee mechanism'; *vide infra*) takes advantage of lead acetate's ($Pb(OAc)_4$) ability to (stoichiometrically) associate with, chelate to, and cyclize with, *specifically*, vicinal diols.[6] The arrived at cyclic lead species eventually collapses, reducing lead from (IV) to (II) and oxidizing both alcohols in the process; which happens to also be accompanied with a C-C bond cleavage (Figure 3, middle). Lastly is the transformation of unactivated alkenes into their corresponding vicinal diols, by treatment with osmium tetroxide (OsO_4). When followed by exposure to a strong stoichiometric oxidant, such as sodium periodate ($NaIO_4$), the vicinal diols are collapsed in a similar manner to that of the 'Criegee-oxidation;' this process is referred to as the 'Lemieux-Johnson' oxidation (Figure 3, bottom).[7]

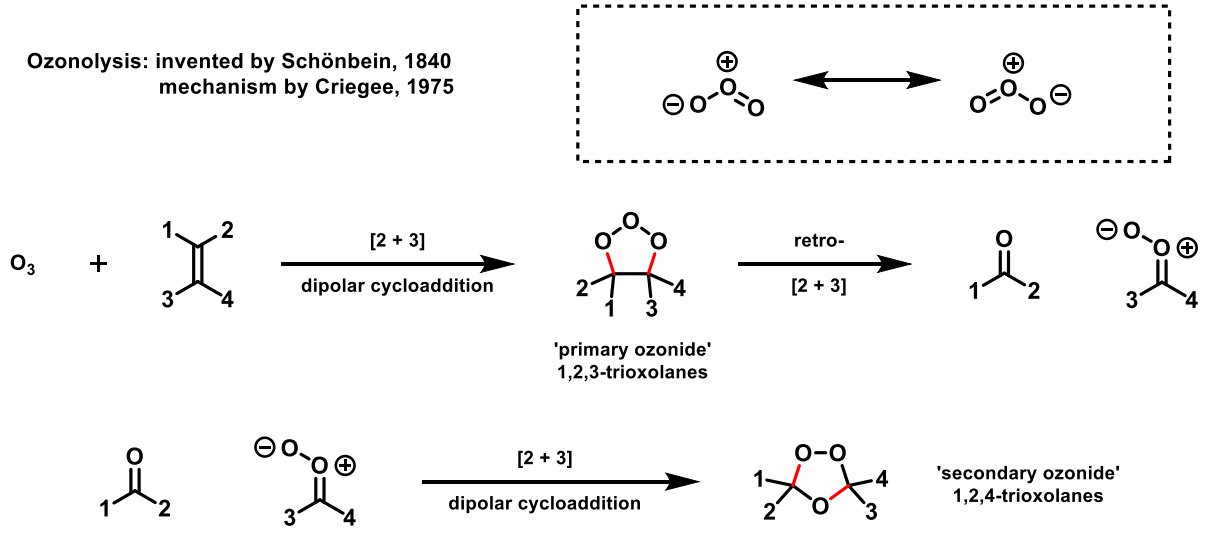
Figure 3. Olefin Oxidations to Afford Ketone Adducts



One other important oxidation reaction, intentionally left out above, would be ozonolysis; the process of oxidatively cleaving a carbon-carbon double bond and as a result forming two carbonyl's in the 'net' overall process. This is achieved *via* the use of ozone (O_3) as the stoichiometric oxidizing reagent. Although this organic reaction was invented back in 1840, by Christian F. Schönbein,[8a] the proper mechanistic understanding of the process, at a molecular level, wasn't fully accepted until a publication by R. Criegee in 1975.[8b] This is an

important reaction in synthesis due to its reliability, generally high yielding reactions, and atom economy. As depicted in Figure 4, this transformation follows a three-step mechanism: (1) initial formation of a 'primary ozonide' *via* a [2 + 3]-dipolar cycloaddition; (2) decomposition of the primary ozonide, *via* a *retro*-[2 + 3] cycloreversion, into a carbonyl compound and a 'carbonyl oxide;' (3) [1,2]-addition of the 'carbonyl oxide' into the carbonyl, through a different [2 + 3]-dipolar cycloaddition, to afford a 'secondary ozonide.' Eventual collapse of the secondary ozonide upon reaction workup with additives such as dimethylsulfide (DMS) or triphenyl phosphine (PPh_3) provides two new carbonyl compounds and the oxide of the additive used (*e.g.* DMSO or $OPPh_3$).

Figure 4. Ozonolysis & its 3-Step 'Criegee' Mechanism



Ozone itself is naturally occurring and serves as a valuable 'sun-block,' not only for mankind, but all of Earth. The ozone-layer, also referred to as the 'ozone-shield,' was discovered in 1913 by French physicists Farby and Buisson.[9a] Formed roughly 20-30 kilometers above the surface of Earth (12-19 miles, or 65,000-100,000 feet) single molecules of oxygen (O_2) are continuously absorbing the strong ultraviolet (UV)-radiation emitted from

the Sun to produce ozone (O_3) and heat; a process referred to as the 'ozone-oxygen cycle' which follows the general sequence shown in Equation 1 below. Proposed by Chapman in 1930 the cycle adopts a three stage 'creation' – 'cycle' – 'removal' mechanism.[9a,b] The term 'cycle' is adequately applied to describe the course of chemical reactions for ozone generation and removal, since this is a 'continual' mechanism. Thus, there is no actual *termination* step; which differentiates this overall sequence of radical cascades from the more traditional radical based chemistry designations of: initiation, propagation, and termination. The total, global, mass of ozone is roughly 3 billion metric tons, a value that remains relatively constant throughout time due to the 'Chapman-cycle.' Although, due to recent effects of global-warming, the depletion or consumption of ozone in our atmosphere, may attribute to lower current levels and incremental decreases in the near future.

Equation 1. Ozone-Oxygen Cycle: 'Chapman-Cycle'

Creation: ----------

$$O_2 + h\upsilon \rightarrow 2\,O\cdot + heat$$

$$O\cdot + O_2 + M \rightarrow O_3 + M$$

Cycle: ----------

$$O_3 + h\upsilon_{(240-310nm)} \rightarrow O_2 + O\cdot$$

$$O_2 + O\cdot \rightarrow O_3 + E_k$$

Removal: ----------

$$O_3 + O\cdot \rightarrow 2\,O_2$$

$$2\,O\cdot \rightarrow O_2$$

(*net removal*) ---------- $2\,O_3 \rightarrow 3\,O_2$ ----------

*** $h\upsilon$ = UV-irradiation, M = a third 'body' which absorbs the excess energy of the process, E_k = kinetic energy***

The use of ozone as a stoichiometric reagent for the generation of a carbonyl group is a fundamental reaction with valuable applications to organic synthesis. Olefin oxidation reactions in numerous total synthesis campaigns, past and present, attest to the impact of this simple, yet powerful transformation; a few exemplary cases are illustrated in Figure 5. Accordingly, the highly potent antimalarial molecule (+)-artemisinin was obtained *via* ozonolysis of a vinylsilane in the last step of an exceptionally concise 10-step synthesis, starting from (*R*)-(+)-pulegone (Figure 5, top).[10a] Thus, a series of protonation's, heterolytic bond breaking, 'Beckman-type' migration ('anionotropic shift'), and rearrangements convert the relatively 'flat' starting vinylsilane into the desired highly complex peroxy-containing

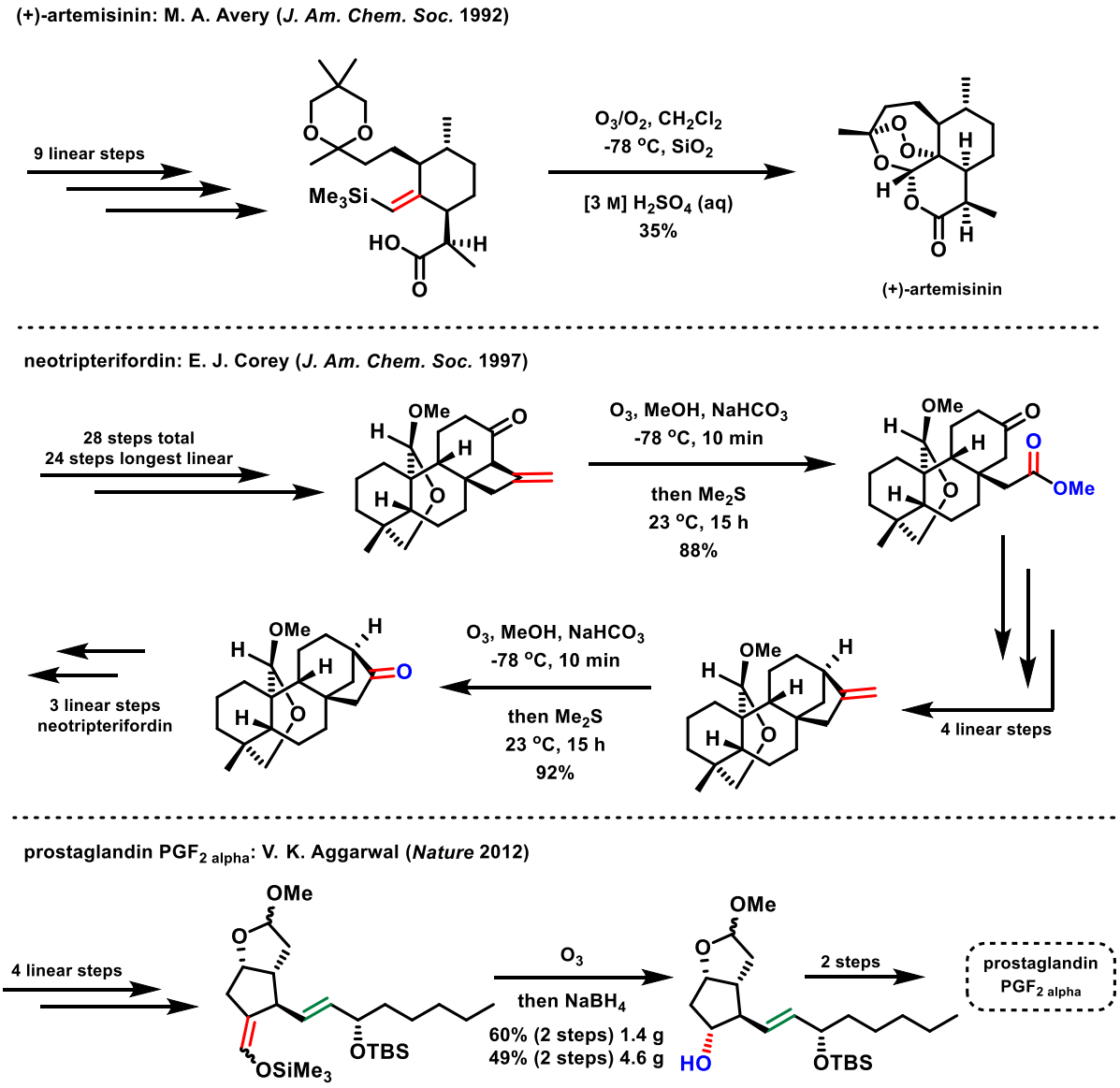
natural product;[10b] a rare example of the exotic fate ozonides can impart to their olefinic substrates.

The natural product neotripterifordin, isolated from the Chinese medicinal plant *Tripterygium wilfordii*, which possesses promisingly enhanced anti-HIV activity employed the use of ozone (O_3) twice in its synthesis.[10c] This publication is of particular note as it is generally referred to as "Aldrich catalogs #1 top desk reference of all time;" including over twenty commonly encountered reactions, with exquisite reproducibility.[10d] The first ozonolysis occurs relatively deep in the synthesis as shown in Figure 5 (middle). Thus, ozonolysis of the advanced pentacyclic derivative's exocyclic-methylene olefin, with concomitant methanol solvolysis of the resulting acyclobutanone intermediate, afforded the ozonolysis adduct as its methyl ester derivative. Four linear synthetic steps later, three steps from the final product, cryogenic ozonolysis was employed again, on yet another exocyclic-methylene, to eventually arrive at the 'proposed' natural product. The success of this synthetic route allowed also for the inversion of stereochemistry at 'C-16,' prompting the revision of neotripterifordin's structure.

Lastly, and perhaps most relevant, is the elegantly compact synthesis of the popular pharmaceutical prostaglandin $PGF_{2\alpha}$ (an analogue of 'latanoprost,' a commercial therapeutic for the treatment of glaucoma, which alone reached sales in excess of $1.75 billion in 2010) by V. K. Aggarwal in 2012 (Figure 5, bottom).[10e] This ingenious, 7-step, retrosynthetic analysis identified an efficient disconnection sequence which revolved around a 'mixed-higher-order-Lipshutz-cuprate' [1,4]-conjugate addition, *in situ* silyl enol ether protection, and subsequent ozonolysis-[1,2]-ketone reduction (with $NaBH_4$). Of specific relevance is that this

'key' ozonolysis, of the *'activated'* silyl enol ether, occurred with complete regioselectivity in the presence of another, unactivated, disubstituted olefin.

Figure 5. Examples of Ozonolysis in Natural Products Total Synthesis



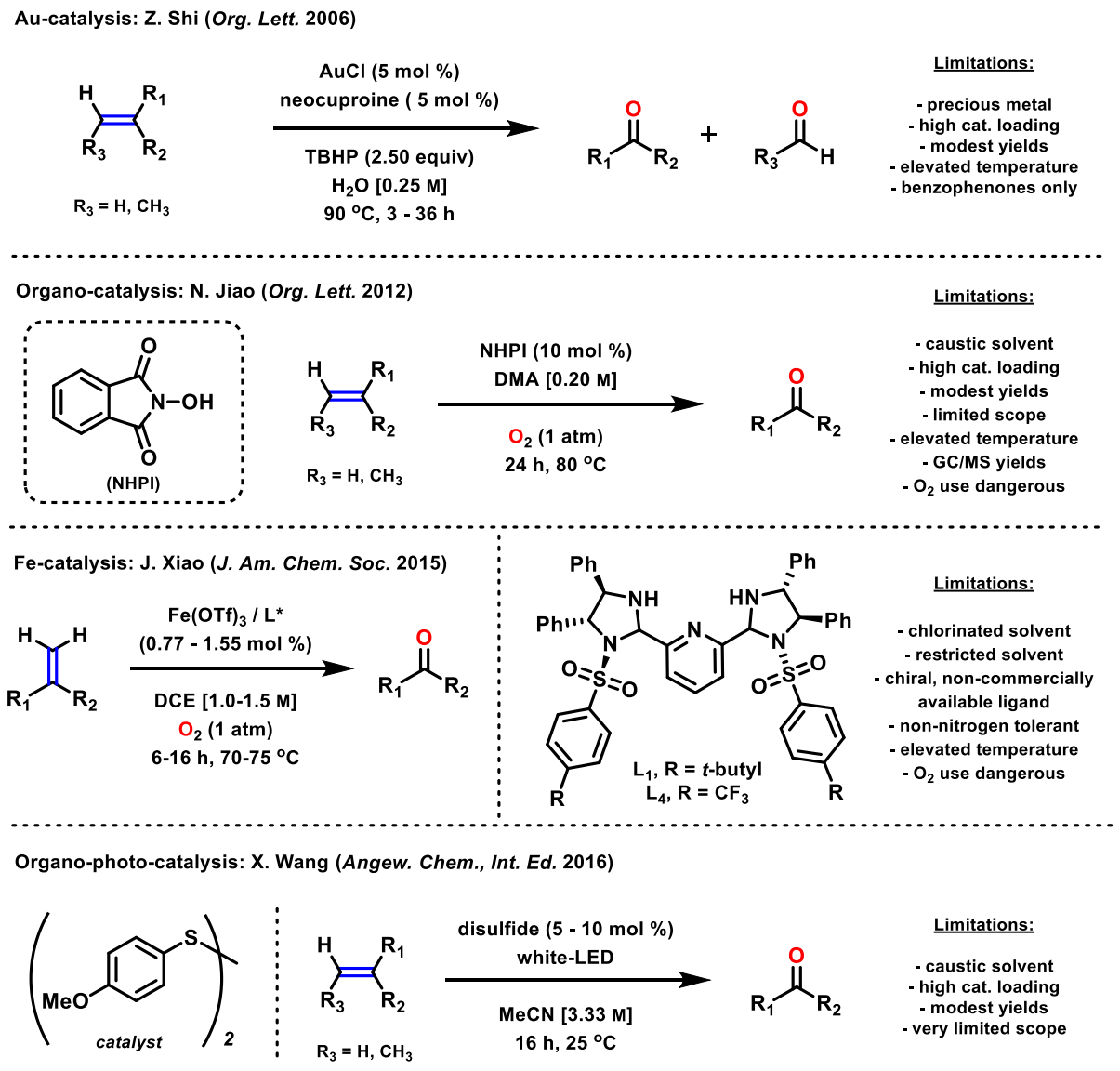
Notwithstanding its time-honored status in the community, safety and handling issues that necessitate specific operational needs present a less than ideal situation. Examples of this are the specialized laboratory equipment for its formation at low (usually cryogenic) temperatures, the inherent toxicity associated with ozone, and the accompanied explosion risks of the resulting ozonides (or excess unreacted ozone) if warmed too quickly or improperly quenched.[11,12]

An equivalent based on catalysis, however, might obviate these shortcomings, allowing for a more practical, safe, and user-friendly approach to this important reaction. Up until recently,[8b,10b,13] there were no reports on methodologies directed specifically to achieve this conversion. Only within the past few years have such reports been successfully conducted under catalytic conditions (Figure 6).

In 2006, Shi and co-workers described a gold-catalyzed oxidative cleavage of simple benzophenone derivatives in water, albeit at 90 ^{o}C.[14] Later, an organocatalytic approach was reported utilizing *N*-hydroxyphthalimide (NHPI or PINO) in dimethylacetamide, at 80 ^{o}C, with *dangerous* molecular oxygen as the oxidant, relying upon GC analysis to determine yields; again providing mainly benzophenone derivatives.[15] More recently, in 2015, Xiao *et. al.* disclosed an elegant methodology based on iron(III) triflate, in hot DCE;[16a] a chlorinated solvent which has recently become a restricted substance in Europe.[16b] This report described a large scope of substrates leading to benzaldehyde, acetophenone, and benzophenone derivatives, although it relied upon the activity of a non-commercially available chiral-pyridine bis-sulfonamide ligand. Moreover, the conditions appeared not to be compatible with nitrogen within the precursor substrates; greatly reducing its attractiveness in directed synthesis. Lastly, in 2016, a photocatalytic approach employing an aromatic disulfide as catalyst was described,

nearly exclusively leading to benzaldehyde products.[17] Thus, a more general methodology that offers room temperature conditions, avoids use of waste-generating organic solvents,[18] relies upon a readily available and earth abundant metal,[19] and involves a simple and safe protocol is still desirable.

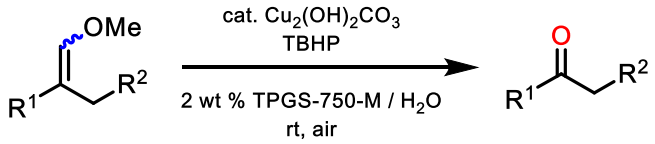
Figure 6. Few Known Catalytic Oxidative-Cleavage Reactions



Past documentation of many radical processes both promoted by, and catalytic in, copper, suggested its potential as a mediator of this transformation. It was anticipated to be an attractive alternative when compared to those metals used previously (*vide supra*) due to coppers' low toxicity, controllable oxidation states, relative abundance, and cost.[20] Since copper has been previously utilized with substantial success in oxidations of alcohols to aldehydes and/or ketones,[21] it was reasonable to anticipate its participation in an oxidative cleavage of alkenes using a peroxide as the stoichiometric oxidant. Initial experiments, inspired by Shi's prior report,[14] suggested that our micellar catalysis technology (*i.e.*, using water at rt) might be amenable.

3.2. Results and Discussion

Scheme 1. General Reaction Developed & Discussed Herein



As shown in Table 1, use of either ligated gold or copper salts, together with a peroxide under micellar catalysis conditions, led to varying amounts of the desired ketone in which copper was found to significantly out-perform gold as the metal catalyst (entries 1 *vs.* 2). These reactions were run 'open-flask,' thereby allowing atmospheric oxygen to participate as needed in the process. Conversely, when the analogous reaction was run under argon, no conversion of the starting α-methylstyrene was observed. However, upon addition of more peroxide (2.00 equiv) and further stirring while open to air, the same reaction began to produce the expected oxidation product (entry 3). Switching from a copper(I) to (II) salt was of little consequence (entries 1 *vs.* 4). Running the reaction with TBHP under one atmosphere of molecular oxygen, likewise, showed no benefit, and in fact, led to inferior results (entry 5). A control reaction run exposed to air, but in the absence of TBHP afforded no reaction (entry 8), while no reaction was observed in the absence of copper (entry 9). Taken together, these data suggest a curious necessity for both an internal stoichiometric oxidant, as well as atmospheric (oxygen) conditions in the presence of a copper salt. From the data in entries 4, 6 and 7, a concentration of 0.75 M was determined to be optimal. Evaluation of several other sources of peroxide surprisingly led to no product formation (entries 12-15). Employment of PIDA

(phenyliodine(III) diacetate), as the stoichiometric oxidant, also did not promote the desired oxidative cleavage (not shown); however, it *did* smoothly provide the product of a 1,2-aryl shift.[22a] Thus, olefin attack of the hypervalent λ^3-iodane, with loss of an acetate ligand, concomitant trapping of the *in situ* generated carbocation with a molecule of adventitious water, ligand dissociation (- OAc^-) with subsequent 1,2-aryl shift, generates a second carbocation which is thus attacked by a second molecule of water, resulting in a *geminal*-diol which, after tautomerization, produces the methyl ketone rearrangement product (Figure 7). Alternatively, one can envision this process also occurring through a more traditional, *in situ* derived, semi-pinacol-type rearrangement.[22b-d] Other copper salts were also screened, with copper hydroxide providing the best results (entry 16). Noteworthy is the role of the surfactant to safely enable this process, (***Warning!*** Explosion risk: deploy a blast shield if uncertain of safety) as in the absence of TPGS-750-M (*i.e.*, the corresponding "on-water" reaction), discontinuation of stirring concentrated the peroxide together with the organic substrate, which quickly led to detonation of the reaction.

Figure 7. Hypervalent Iodine(III) Mediated 1,2-Aryl Shift in TPGS-750-M

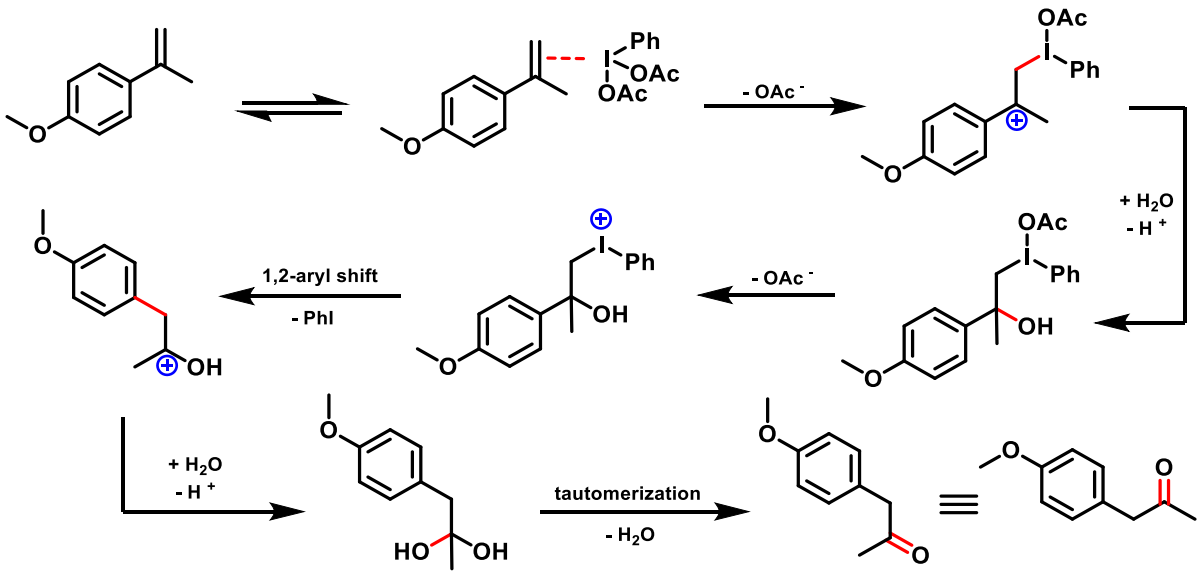
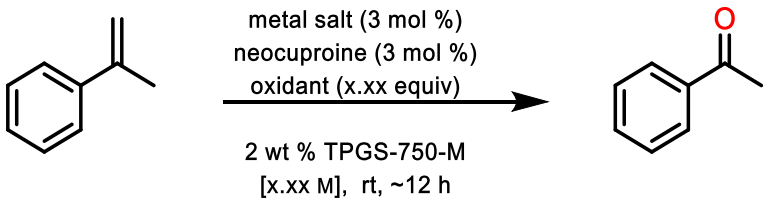


Table 1. Initial Optimization Screening of Reaction Parameters with α-Methylstyrene

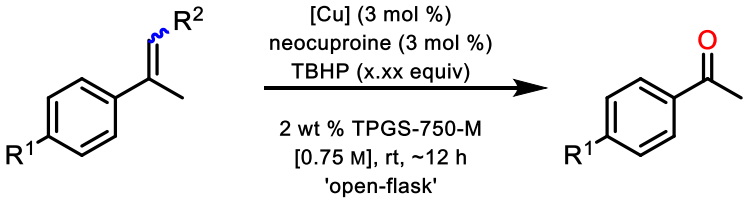


entry	metal/ L	oxidant (equiv)	yield[a] (%)
1	Cu(I)OAc	TBHP (2.00)	57
2	$AuCl_3$	TBHP (2.00)	26
3[b]	Cu(I)OAc	TBHP (2.00)	NR (47)[c]
4	$Cu(OAc)_2$	TBHP (2.00)	59
5[d]	$Cu(OAc)_2$	TBHP (2.00)	48
6[e]	$Cu(OAc)_2$	TBHP (2.00)	16
7[f]	$Cu(OAc)_2$	TBHP (2.00)	13
8	$Cu(OAc)_2$	none	NR
9	none	TBHP (2.00)	NR
10	$Cu(MeCN)_4PF_6$	TBHP (2.00)	55
11	Cu(*i*-butyrate)$_2$	TBHP (2.00)	39
12	$Cu(OAc)_2$	H_2O_2 (3.00)	NR
13	$Cu(OAc)_2$	cumene-OOH (2.00)	NR
14	$Cu(OAc)_2$	TMS-O-O-TMS (2.00)	NR
15	$Cu(OAc)_2$	MCPBA (2.00)	NR
16	$Cu(OH)_2$	TBHP (2.50)	65
17	CuO	TBHP (2.50)	48

[a] Yield of isolated products, after column chromatography. [b] Reaction initially run under Ar. [c] Reaction yield after additional TBHP with exposure to air. [d] Reaction run under 1 atm of O_2. [e] Concentration of [0.50 M]. [f] Concentration of [1.00 M]. NR = no reaction.

To further study the reactivity of alkenes towards an ostensible electrophilic oxygen source, various substitutions at the -R^2 position were assessed (Table 2). Thus, utilizing *p*-methoxy- and *p*-bromo-α-methylstyrene as baseline cases (entries 1, 2; R^2 = H), the addition of alkyl chains (either methyl or *n*-pentyl groups) resulting in more bulky trisubstituted alkenes (entries 3 and 4; respectively) had a negative impact on reaction efficiency. Surprisingly, placement of a 4-methoxyphenyl group, again, at the activating -R^2 position completely shut down the reaction (entry 5). This is in line with the observation that simple, mono-alkenyl-substituted styrenes also do not undergo oxidation under these conditions, suggesting the potential for an orthogonal strategy towards selective ketone formation. Gratifyingly, use of the corresponding methyl enol ether provided a marked improvement (entries 6 and 7).[10e] Decreasing the amount of TBHP by half (to 1.25 equivalents) did not effect the overall extent of reaction (entries 7 *vs.* 8). The control experiment without ligand was particularly informative, as use of the cupric salt alone was shown to be equally or even more effective than its use in ligated form (entries 8 *vs.* 10). Based on the results using the more basic copper hydroxide relative to copper acetate (65% *vs*. 59%; Table 1, entries 16 *vs.* 4), the carbonate salt of intermediate basicity[23] was then assessed (Table 2, entry 11). These results indicated that the study should be continued using this source of copper(II). Lowering the catalyst loading to either 1 or 2 mol % gave slightly diminished yields, whereas increasing the loading from 3 to 5 mol % showed no observed benefit (entries 11-14).

Table 2. Screening of Basic Copper Salts & Effect of Olefin-Activating Group



entry	3 mol % [Cu] / L	R^1	R^2	TBHP (equiv)	yield[a] (%)
1	$Cu(OH)_2$ / L	OMe	H	2.50	55
2	$Cu(OH)_2$ / L	Br	H	2.50	48
3	$Cu(OH)_2$ / L	OMe	Me	2.50	31
4	$Cu(OH)_2$ / L	OMe	$-C_5H_{11}$	2.50	36
5	$Cu(OH)_2$ / L	Br	*p*-MeO-C_6H_4	2.50	NR
6	$Cu(OH)_2$ / L	OMe	OMe	2.50	69
7	$Cu(OH)_2$ / L	Br	OMe	2.50	66
8	$Cu(OH)_2$ / L	Br	OMe	1.25	67
9[b]	$Cu(OH)_2$ / L	Br	OMe	1.25	70
10	$Cu(OH)_2$	Br	OMe	1.25	73
11	$Cu_2(OH)_2CO_3$	Br	OMe	1.25	84
12[c]	$Cu_2(OH)_2CO_3$	Br	OMe	1.25	62
13[d]	$Cu_2(OH)_2CO_3$	Br	OMe	1.25	67
14[b]	$Cu_2(OH)_2CO_3$	Br	OMe	1.25	84
15[e]	$Cu_2(OH)_2CO_3$	Br	OMe	1.25	70
16[f]	$Cu_2(OH)_2CO_3$	Br	OMe	1.25	79
17[g]	$Cu_2(OH)_2CO_3$	Br	OMe	1.25	78
18[g]	$Cu_2(OH)_2CO_3$	Br	OMe	none	NR

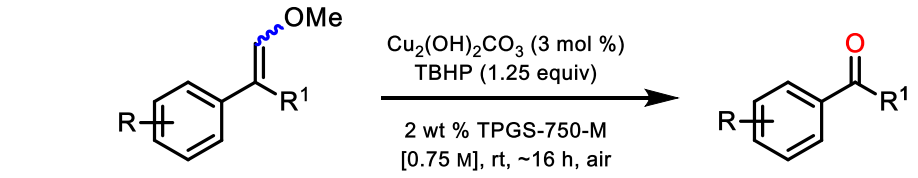
[a] Yield of isolated products, after column chromatography. [b] 5 mol % catalyst. [c] 1 mol % catalyst. [d] 2 mol % catalyst. Reaction run: [e] in 1,2-dichloroethane. [f] in acetonitrile. [g] under 1 atm of O_2.

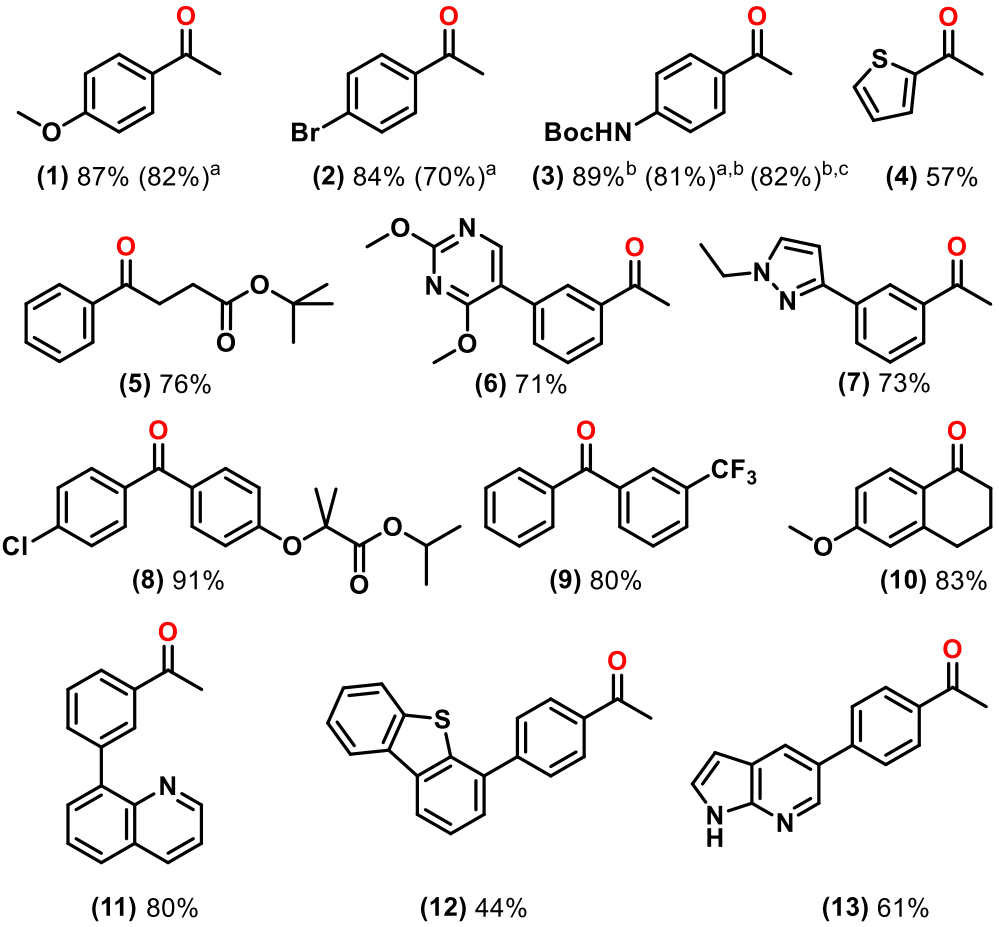
When the solvent was changed to either 1,2-dichloroethane[16b] or acetonitrile, common organic solvents for this type of transformation,[16a,17] the reactions proceeded reasonably well; however; they led to somewhat lower levels of conversion than those observed in TPGS-750-M/water (entries 11 *vs.* 15, 16). Lastly, experiments utilizing one atmosphere of oxygen, with or without TBHP, afforded inferior results (entries 17 and 18; respectively).

Based on these optimized conditions, the generality of the catalyst system was assessed on an array of aryl/alkyl methyl enol ethers (Scheme 2). *E/Z*-Mixtures of α-methyl-substituted educts with aryl groups containing either electron-donating or -withdrawing substituents were found to readily participate (*e.g.* **1** – **3**) with substitution at the *ortho*-, *meta*-, or *para*- positions (*e.g.* **10**, **6**, **13**; respectively). Several heterocyclic derivatives reacted without incident under these conditions, including those containing a thiophene, pyrazole, pyrimidine, azaindole, dibenzothiophene, or quinoline moiety, without compromising the (nonligated) copper catalyst. Furthermore, substrates containing extended alkyl chains (*e.g.*, leading to product **5**), as well as cyclic arrays (*e.g.*, **10**) gave the desired ketones in good yields, each representing a substitution pattern that has not been found in prior reports.[13d,14,15,16a,17] 1,1-Diarylalkenyl enol ethers also smoothly formed several benzophenone derivatives in good yields, as in products **8** and **9**. The former, fenofibrate (**8**), is used for treatment of hypercholesterolemia and hypertriglyceridemia.[24] It is noteworthy that under the aqueous conditions employed, the

methyl enol ether group was not observed to undergo hydrolysis to the corresponding aldehyde.

Scheme 2. Scope of Aryl/Alkyl Enol Ether Oxidations

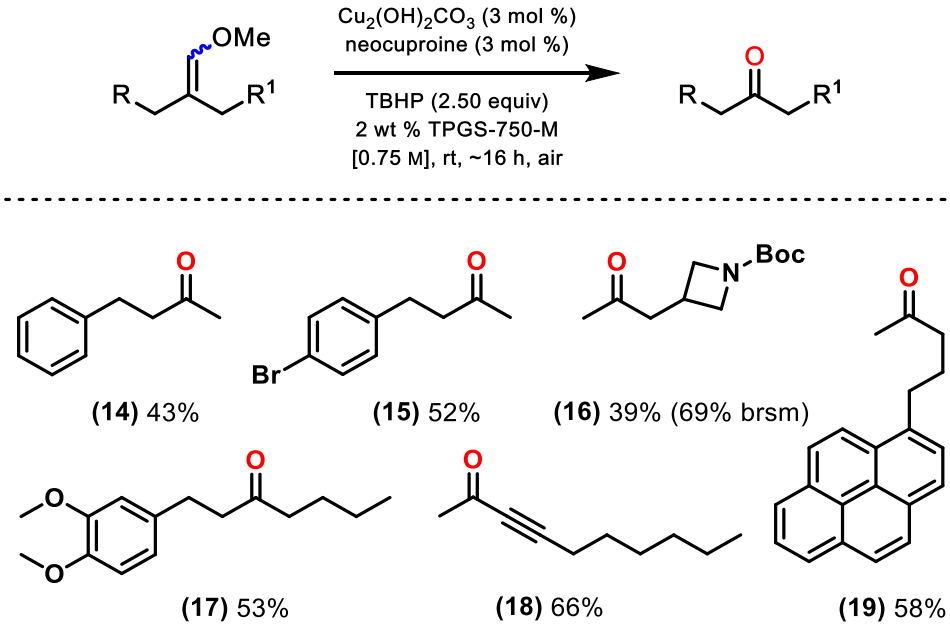




*** [a] Isolated yield of reaction run with 3 mol % $Cu(OH)_2$. [b] 10 % v/v THF added to increase homogeneity. [c] Isolated yield of reaction run at 1.00 mmol scale.

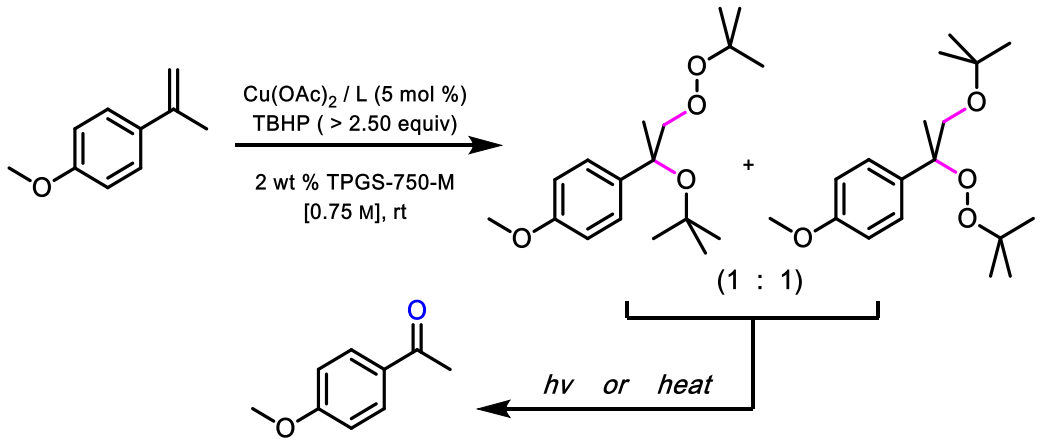
Extension to more challenging and previously unreported catalytic oxidative cleavage reactions of dialkyl olefins was next pursued (Scheme 3). By applying conditions similar to those shown in Scheme 2, only low yields of product ketone were initially observed. For this class of substrate increasing the amount of oxidant from 1.25 to 2.50 equivalents provided a more effective combination. In most cases, although full consumption of starting materials was observed, isolated yields were consistently in the moderate category. Benzylacetone derivatives **14** and **15** were readily formed under these mild conditions. Extending the distance of the alkyl chain in pyrene-derivative **19** proceeded smoothly, likewise increasing the alkyl chain length, *e.g.*, from methyl to *n*-butyl (leading to product **17**), gave comparable yields. The presence of nitrogen, protected as its -Boc derivative, in azetidine-containing product **16** was also tolerated, although the level of conversion was lower leading to a diminished isolated yield. Interestingly, the use of an unsaturated precursor ultimately affording a conjugated ketone (as in **18**) led to a somewhat improved outcome.

Scheme 3. Preliminary Scope of Alkyl/Alkyl Oxidations



Nonproductive pathways leading to undesired intermediates include a Kharasch-type mechanism, where allylic oxidation with a *t*-butoxy or *t*-butylperoxy radical could trap the intermediate olefinic radical prior to addition of molecular oxygen.[25] Indeed, this type of by-product formation was observed in initial studies with 4-methoxy-α-methylstyrene (Figure 8). Such an alternative, and competitive pathway is similar to that seen long ago by Kochi,[26] and to some extent, more recently by Wang and co-workers.[17]

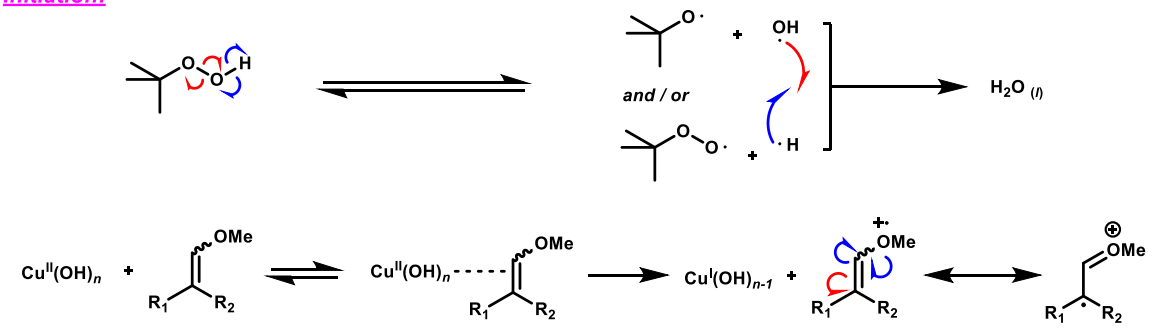
Figure 8. Competitive Potential Kharasch-type Allylic Oxidation



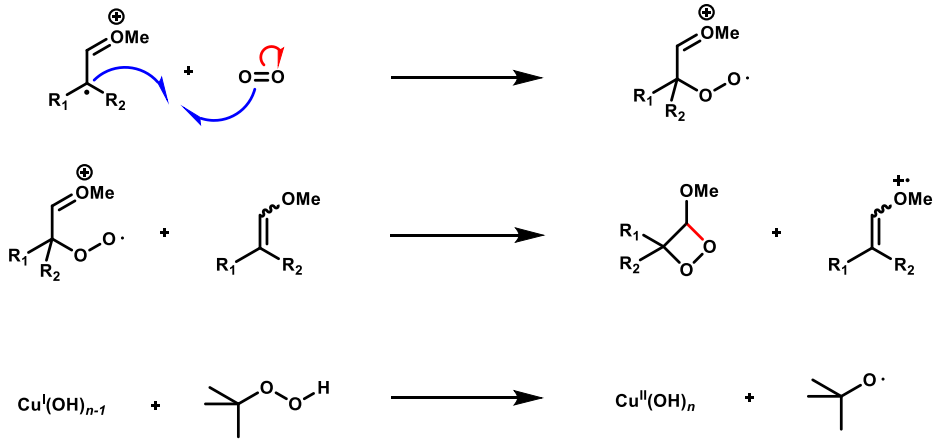
When the pure 'by-product' was isolated and then, as a mixture with authentic material, analyzed by GC/MS, the chromatograms showed a single peak with an *m/z* corresponding to the desired ketone. Moreover, heating this by-product neat for 30 seconds led to a rapid, auto-catalytic reaction, with subsequent proton NMR analysis now showing a roughly 1:1 mixture of both product ketone and peroxy by-product.[27] Thus, this presumed double Kharasch intermediate undergoes either electrochemical (GC filament ionization) or thermal (heat-gun) collapse to the desired ketone. Collectively, the experimental data suggest a plausible mechanism for radical-based cooperativity, akin to that described decades ago for enamine's engaging molecular oxygen (Equation 2, below).[28]

Equation 2. Proposed Mechanistic Radical Pathways: Initiation, Propagation, and Termination

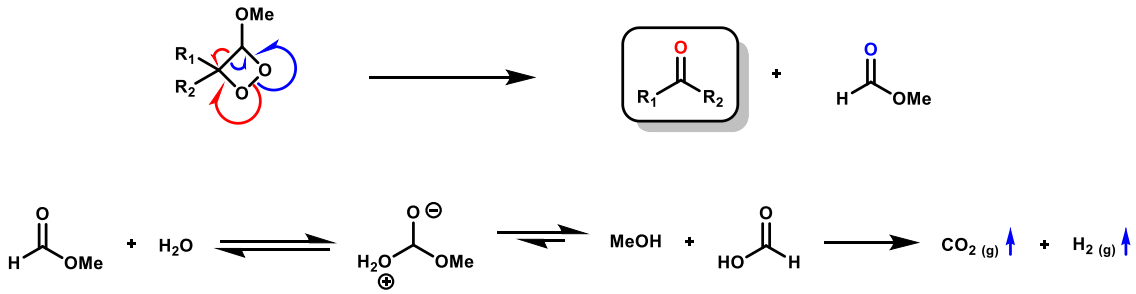
Initiation:



Propagation:



Termination:



3.3. Conclusion

In summary, a mild, safe, and green protocol for converting methyl enol ethers into their corresponding ketone derivatives that avoids low temperature ozonolysis has been developed. The technology avoids precious metal catalysis, utilizing an inexpensive Cu(II) salt enabled by micellar catalysis in water at room temperature. This methodology compares very favorably with existing catalytic oxidative cleavage reactions in terms of generality, and aids in further extending the substrate scope beyond prior art that was limited to formation of products in the acetophenone and benzophenone series. In the composite, these preliminary results offer considerable promise for further developments, aimed at addressing this textbook reaction in organic synthesis.

Further developments will likely aim to address the following current limitations:

1) Use of other oxidants, in place of a peroxide; ideally being less than stoichiometric. Here a reliable radical relay source that could act as a co-catalyst, re-oxidizing copper and itself being reduced in the process, which after reduction is aerobically oxidized to restore its oxidation potential would be ideal. A concept similar to that of Nature's $NADP^+$/NADPH co-factor cycle. Or through an electrochemical, anode/cathode, process.

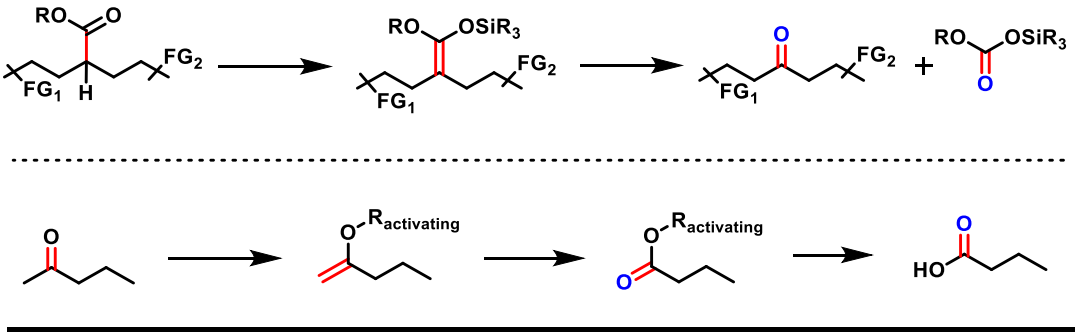
2) Improvements upon TLC profile. Even high yielding reactions can produce complex TLC analyses; as well even resulting *tert*-butanol stains strongly with vanillin-stain (light red coloration) which can lead the chemist astray from time-to-time. The use of

a work-up additive, as DMS or PPh_3 have been employed in traditional ozonolysis, helping to break-down any 'trapped' (cyclic)peroxy-intermediates.

3) Perhaps increasing the 'activation' of the dialkyl cases further *via* a *geminal*-diolate; formed *via* α-deprotonation of an α,α^1 -disubstituted ester followed by protection of a properly chosen 'secondary' activating group (Figure 9).

4) Lastly, due to the radical nature (at least to some extent) the aid of photons in the source of strong UV-light may lead to benefits by overcoming reaction coordinate energy barriers.

Figure 9. Double-Olefin Activation/ 'Burning-a-Carbon'



3.4. References

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12. For a recent report of improper ozone quenching and the associated results see: https://cls.ucla.edu/lessons-learned/lessons-learned-fire/248-three-researchers-exposed-to-barium-oxide-during-spill-clean-up-2.
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27. See experimental spectra section for ^{1}H NMR over-lay spectra of 'heat-gun' experiment.

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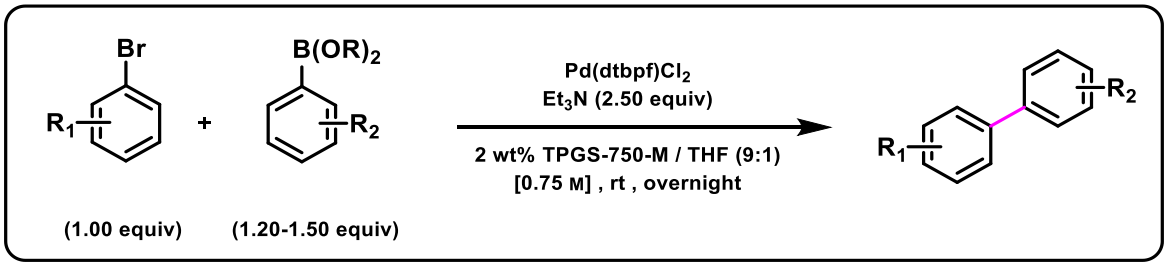
3.5. Experimental Data

1. Synthetic Details

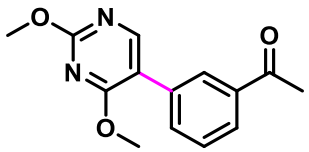
General procedure: Synthesis of precursors *via* 'Suzuki-Miyaura' [2]



To a dry round bottom flask charged with a magnetic stir bar was added the aryl bromide (1.00 equiv), the corresponding boron nucleophile (1.20-1.50 equiv), and Pd(dtbpf)Cl_2 (2-5 mol %). The sealed flask was purged with argon (3 times). Under a positive flow of argon was added a solution of 2 wt % TPGS-750-M, ~[0.75 M], with 10 v/v % of THF. After stirring at rt for ~10 minutes, dry Et_3N (2.50 equiv) was introduced slowly, washing the walls of the flask to bring all solids into solution. The resulting mixture was then stirred at rt overnight (~12-16 h). Once complete, determined by TLC analysis, the reaction was diluted with EtOAc and stirred for ~5-10 min, followed by direct transfer to a separation funnel. The organic layer was washed with brine (3 x 20 mL) then with distillated water (1 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *via* rotary evaporation. Products were purified *via* column chromatography on silica gel (see below) to afford the desired compound.

1-(3-(2,4-Dimethoxypyrimidin-5-yl)phenyl)ethan-1-one (6)

Notebook: PTS-1-068-2



Prepared according to the general 'Suzuki-Miyaura' procedure above, 3.00 mmol, scale using 3-bromoacetophenone and 2,4-dimethoxypyrimidine-5-boronic acid.

Purification: column chromatography on silica gel, eluting with 30% (EtOAc : hexanes), afforded the desired compound as a beige solid, 634 mg, 82%.

TLC: R_f = 0.35 (30% EtOAc : hexanes), UV, I_2, vanillin stain (orange spot)

^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.08 (s, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 4.04 (d, *J* = 9.4 Hz, 6H), 2.63 (s, 3H)

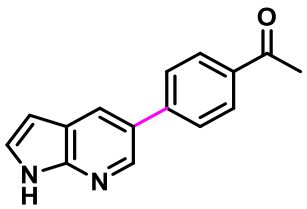
^{13}C NMR: (151 MHz, $CDCl_3$) δ 198.0, 168.3, 165.0, 157.9, 137.5, 134.1, 133.6, 128.9, 128.8, 127.7, 115.5, 55.1, 54.4, 26.9

IR: 3031, 2989, 2958, 1679, 1596, 1555, 1383, 1274 cm^{-1}

HRMS: (ESI) calculated for [$C_{14}H_{14}N_2O_3$]: 259.1083 $[M+H]^+$, found 259.1090

1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)ethan-1-one (13)

Notebook: PTS-1-067-1



Prepared according to the general 'Suzuki-Miyaura' procedure above, 3.00 mmol, scale using 5-bromo-7-azaindole and 4-acetylphenyl boronic acid.

Purification: column chromatography on silica gel, eluting with 100% (EtOAc), afforded the desired compound as a light beige solid, 550 mg, 78%.

TLC: R_f = 0.55 (100% EtOAc), UV, I_2, vanillin stain (blue spot)

^{1}H NMR: (500 MHz, DMSO-d_6) δ 11.82 (s, 1H), 8.60 (s, 1H), 8.31 (s, 1H), 8.04 (d, J = 7.9 Hz, 2H), 7.88 (d, J = 7.9 Hz, 2H), 7.55 (s, 1H), 6.53 (s, 1H), 2.61 (s, 3H)

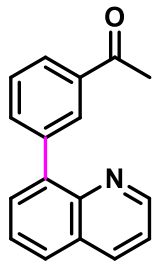
^{13}C NMR: (126 MHz, DMSO-d_6) δ 197.5, 148.4, 143.7, 141.6, 135.1, 129.0, 127.3, 126.8, 126.5, 119.7, 100.4, 26.7

IR: 3712, 3109, 2974, 2922, 2860, 1679, 1596, 1269, 1035 cm^{-1}

HRMS: (ESI) calculated for [$C_{15}H_{12}N_2O$]: 237.1028 [M+H]$^+$, found 237.1039

1-(3-(Quinolin-8-yl)phenyl)ethan-1-one (11)

Notebook: PTS-1-075-1



Prepared according to the general 'Suzuki-Miyaura' procedure above, 4.00 mmol, scale using 8-quinolinylboronic acid and 3-bromoacetophenone.

Purification: column chromatography on silica gel, eluting with 30% (EtOAc:hexanes), afforded the desired compound as a light tan solid, 667 mg, 68%.

TLC: R_f = 0.47 (30% EtOAc : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.94 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.30 (td, *J* = 1.8, 0.5 Hz, 1H), 8.23 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.02 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H), 7.93 (ddd, *J* = 7.6, 1.8, 1.2 Hz, 1H), 7.87 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.76 (dd, *J* = 7.1, 1.5 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 2.66 (s, 3H)

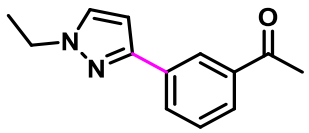
^{13}C NMR: (126 MHz, $CDCl_3$) δ 198.4, 150.6, 146.0, 140.1, 139.9, 137.1, 136.5, 135.5, 130.8, 130.5, 128.9, 128.3, 128.2, 127.4, 126.4, 121.3, 26.9

IR: 3706, 3675, 2974, 2875, 1684, 1056, 1035 cm^{-1}

HRMS: (ESI) calculated for $[C_{17}H_{13}NO]$: 248.1075 $[M+H]^+$, found 248.1084

1-(3-(1-Ethyl-1*H*-pyrazol-3-yl)phenyl)ethan-1-one (7)

Notebook: PTS-1-075-2



Prepared according to the general 'Suzuki-Miyaura' procedure above, 3.00 mmol scale, using 1-ethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole and 3-bromoacetophenone.

Purification: column chromatography on silica gel, eluting with 30% (EtOAc:hexanes), afforded the desired compound as a faint bronze oil, 556 mg, 87%.

TLC: R_f = 0.45 (30% EtOAc : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.65 – 7.53 (m, 3H), 6.29 (m, 1H), 4.10 (q, *J* = 6.2 Hz, 2H), 2.55 (s, 3H), 1.30 (t, *J* = 6.1 Hz, 3H)

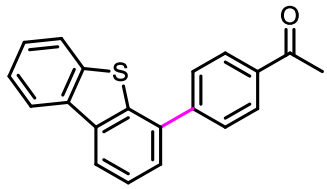
^{13}C NMR: (151 MHz, $CDCl_3$) δ 197.6, 142.1, 138.9, 137.7, 133.4, 131.7, 129.2, 128.7, 128.4, 106.5, 44.7, 26.8, 15.9

IR: 2979, 2942, 1684, 1357, 1258, 780 cm^{-1}

HRMS: (ESI) calculated for $[C_{13}H_{14}N_2O]$: 215.1184 $[M+H]^+$, found 215.1189

1-(4-(Dibenzo[*b*,*d*]thiophen-4-yl)phenyl)ethan-1-one (12)

Notebook: PTS-1-076-2



Prepared according to the general 'Suzuki-Miyaura' procedure above, 3.00 mmol scale, using 4-dibenzothienylboronic acid and 4-bromoacetophenone.

Purification: column chromatography on silica gel, eluting with 20% (EtOAc : hexanes), white solid, 820 mg, 90%.

TLC: R_f = 0.41 (20% EtOAc:hexanes), UV, I_2

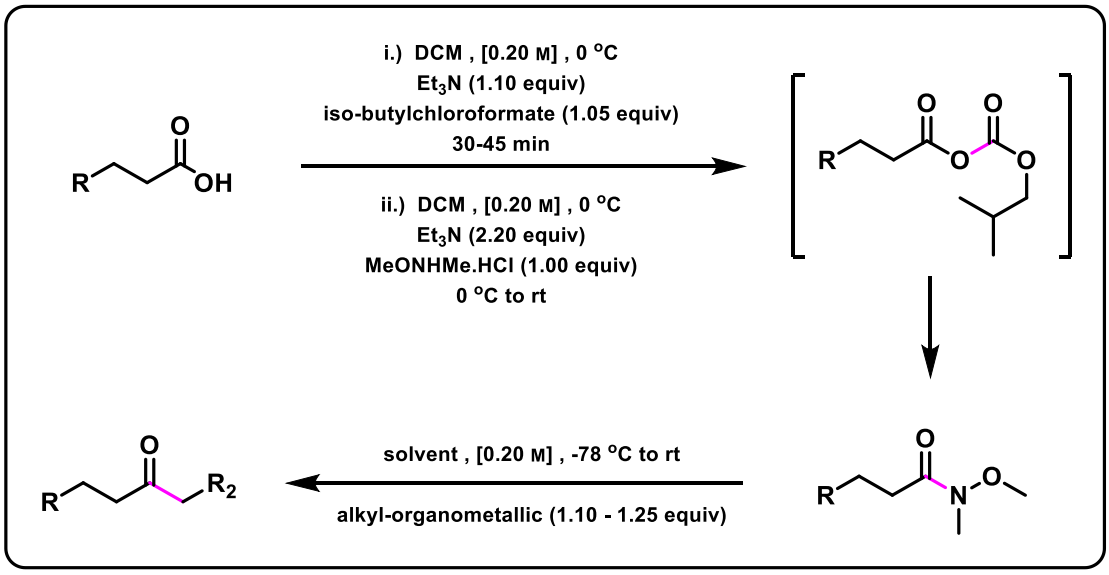
^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.20 (m, 2H), 8.12 (m, 2H), 7.91 – 7.76 (m, 3H), 7.58 (m, 1H), 7.53 – 7.45 (m, 3H), 2.68 (s, 3H)

^{13}C NMR: (151 MHz, $CDCl_3$) δ 197.6, 145.3, 139.4, 138.4, 136.5, 135.8, 135.6, 128.9, 128.5, 127.0, 126.9, 125.2, 124.6, 122.6, 121.8, 121.2, 26.7

IR: 3047, 2989, 1677, 1601, 1257, 750 cm^{-1}

HRMS: (ESI) calculated for $[C_{20}H_{14}SO]$: 302.0765 $[M]^+$, found 302.0778

General procedure: Synthesis of intermediates *via* mixed anhydride/Weinreb amide protocol [3]

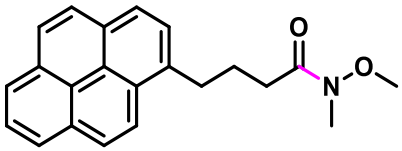


To a solution of the carboxylic acid in DCM, [0.20 M], cooled to 0 °C was added triethyl amine (1.10 equiv) dropwise and the mixture was stirred ~10-15 min. Then, dropwise addition of isobutyl chloroformate (1.05 equiv) was performed (with a vent needle) and the reaction was allowed to stir for 45-60 min. In a separate RBF, MeONHMe•HCl (Weinreb's salt, 1.00 equiv) was dissolved in DCM, [0.20 M], neutralized with excess triethylamine (2.20 equiv) and allowed to stir for ~30 min at rt. The latter (Weinreb salt) solution was then transferred dropwise to the former solution (containing the mixed anhydride), at 0 °C, and stirred until TLC analysis had indicated complete conversion (~2 h to overnight). The reaction was then quenched with DI water, followed by transfer to a separatoy funnel. The aqueous layer was extracted (x 2-3) with DCM, the combined organic layers were then washed with aqueous brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material

was subsequently purified by column chromatography on silica gel (see below) to afford the desired Weinreb amide.

***N*-Methoxy-*N*-methyl-4-(pyren-1-yl)butanamide**

Notebook: DJL-7-135



Prepared according to general procedure above, 7.00 mmol scale.

Purification: column chromatography on silica gel, eluting with 40% then 50% (EtOAc : hexanes), afforded the desired compound as a viscous oil, 1,826 mg, 79%.

TLC: R_f = 0.16 (30% EtOAc : hexanes), UV

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 9.3 Hz, 1H), 8.16 (m, 2H), 8.14 – 8.10 (m, 2H), 8.03 (d, *J* = 2.3 Hz, 2H), 7.99 (t, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 3.59 (s, 3H), 3.45 – 3.40 (m, 2H), 3.21 (s, 3H), 2.58 (t, *J* = 7.3 Hz, 2H), 2.26 – 2.19 (m, 2H)

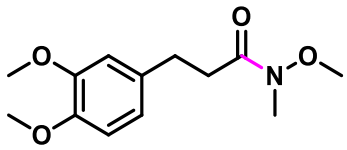
^{13}C NMR: (126 MHz, $CDCl_3$) δ 136.4, 131.5, 131.1, 130.00, 129.0, 127.6, 127.5, 127.4, 126.7, 125.9, 125.2, 125.1, 124.9, 124.9, 124.8, 123.7, 61.3, 33.1, 32.4, 31.5, 26.5

IR: 3047, 2942, 2872, 1654, 1386, 1176, 849 cm^{-1}

HRMS: (ESI) calculated for [$C_{22}H_{21}NO_2$]: 332.1650 $[M+H]^+$, found 332.1663

3-(3,4-Dimethoxyphenyl)-*N*-methoxy-*N*-methylpropanamide

Notebook: DJL-7-212



Prepared according to general procedure above, 25.00 mmol scale.

Purification: After aqueous work-up, a single filtration through a short plug of silica gel afforded the desired compound as a pale-yellow oil, 5,101 mg, 81%.

TLC: R_f = 0.19 (30% EtOAc : hexanes), UV

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.80 – 6.75 (m, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.60 (s, 3H), 3.17 (s, 3H), 2.90 (t, J = 7.8 Hz, 2H), 2.72 (t, J = 7.9 Hz, 2H)

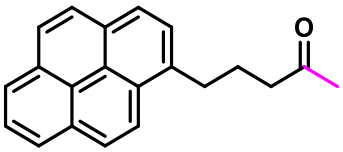
^{13}C NMR: (126 MHz, $CDCl_3$) δ 149.0, 147.5, 134.1, 120.3, 112.0, 112.0, 111.4, 111.4, 61.3, 56.0, 56.0, 34.1, 32.3, 30.4

IR: 2995, 2936, 2837, 1665, 1514, 1257, 1234, 1024 cm^{-1}

HRMS: (ESI) calculated for [$C_{13}H_{19}NO_4$]: 276.1212 [M+Na]$^+$, found 276.1201

5-(Pyren-1-yl)pentan-2-one (19) [4]

Notebook: DJL-7-138



Step II:

To a RBF containing the corresponding Weinreb amide (3.00 mmol) dissolved in dry ether, [0.20 M], at -78 °C, was added dropwise a solution of methylmagnesium chloride (1.50 equiv). The reaction was allowed to stir until it had reached ~0 °C, at which point TLC analysis indicated a complete reaction. Then the reaction was quenched with HCl [1 N] (1.10 equiv), introduced slowly. The crude reaction mixture was transferred to a separatory funnel and extracted with ether (x 2); the combined organic layers were then washed with aqueous brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was subsequently purified by column chromatography on silica gel, eluting with 40% (ether : hexanes), afforded the desired compound as a viscous oil, 661 mg, 77%.

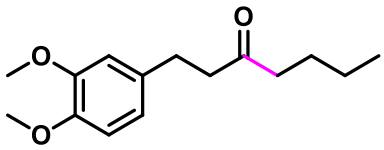
TLC: R_f = 0.27 (40% ether : hexanes), UV

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 9.2 Hz, 1H), 8.20 – 8.15 (m, 2H), 8.12 (m, 2H), 8.05 – 7.97 (m, 3H), 7.85 (d, *J* = 7.8 Hz, 1H), 3.36 (m, 2H), 2.55 (m, 2H), 2.20 – 2.12 (m, 5H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 208.8, 136.1, 131.6, 131.1, 130.1, 129.0, 127.6, 127.5, 127.5, 126.9, 126.0, 125.3, 125.2, 125.1, 124.9, 124.9, 123.5, 43.1, 32.7, 30.2, 25.7

1-(3,4-Dimethoxyphenyl)heptan-3-one (17)

Notebook: DJL-7-222



Step II:

To a RBF containing the corresponding Weinreb amide (10.27 mmol) dissolved in dry THF, [0.20 M], at -78 °C, was added dropwise a solution of *n*-BuLi (1.10 equiv). The reaction was allowed to stir until it had reached ~0 °C, at which point TLC analysis indicated a complete reaction. Then the reaction was quenched with saturated aqueous ammonium chloride, introduced slowly. The crude reaction mixture was transferred to a separatory funnel and extracted with ether (x 2-3); the combined organic layers were then washed with aqueous brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was subsequently passed through a short plug of silica gel with ether, affording the title compound as a viscous yellow oil, 2.400 g, 93%. No further purification was required.

TLC: R_f = 0.54 (60% ether : hexanes), UV, I_2, vanillin stain (violet spot)

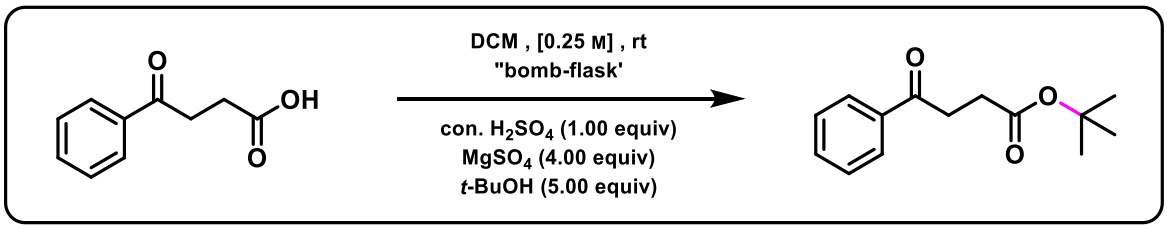
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.77 (m, 1H), 6.70 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.83 (t, *J* = 7.6 Hz, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.37 (t, *J* = 7.4 Hz, 2H), 1.56 – 1.49 (m, 2H), 1.31 – 1.24 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 210.6, 149.0, 147.5, 134.0, 120.2, 111.9, 111.4, 56.0, 55.9, 44.6, 42.9, 29.6, 26.0, 22.4, 13.9

IR: 2958, 2937, 2870, 1716, 1513, 1258, 1237, 1035 cm^{-1}

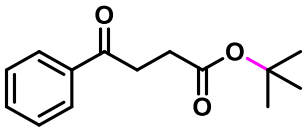
HRMS: (ESI) calculated for [$C_{15}H_{22}O_3$]: 250.1569 [M]$^+$, found 250.1572

Procedure for *tert*-butyl ester protection [5]



***tert*-Butyl 4-oxo-4-phenylbutanoate (5)**

Notebook: DJL-6-300, PTS-1-044



To a 'bomb-flask' containing anhydrous $MgSO_4$ (4.00 equiv), suspended in dry DCM, ~[0.25 M], at rt was added dropwise concentrated sulfuric acid (1.00 equiv), and the resulting slurry was stirred for 15-20 min. Then the carboxylic acid (1.00 equiv) was introduced in a single portion, followed directly by *tert*-butanol (5.00 equiv); the resulting mixture was stoppered tightly, sealed with Teflon tape, and allowed to stir at rt overnight, ~12-16 h. The reaction was then carefully, and *slowly*, quenched with aqueous saturated $NaHCO_3$ (in a vessel large enough to accommodate strong-vigorous bubbling) until all of the magnesium sulfate has dissolved. The crude reaction mixture was transferred to a separatory funnel and extracted with ether (x 2); the combined organic layers were then washed with aqueous brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was subsequently

purified by column chromatography on silica gel, eluting with 15% then 20% (ether : hexanes), to afford the desired compound as a clear viscous oil, 32-64%.

TLC: R_f = 0.22 (10% ether : hexanes), UV, I_2, vanillin stain (forest/olive green spot)

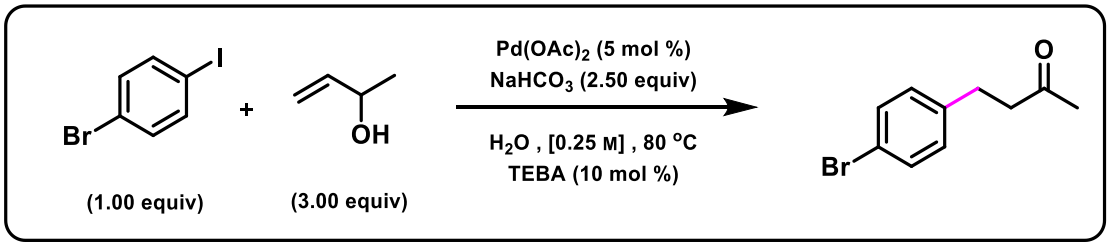
^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 2H), 7.59 – 7.51 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 3.25 (t, *J* = 6.7 Hz, 2H), 2.68 (t, *J* = 6.7 Hz, 2H), 1.45 (s, 9H)

^{13}C NMR: (151 MHz, $CDCl_3$) δ 198.5, 172.3, 136.9, 133.2, 128.7, 128.2, 80.7, 33.6, 29.6, 28.2

IR: 2979, 2922, 1731, 1684, 1367, 1149 cm^{-1}

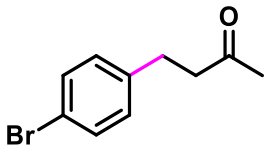
HRMS: (ESI) calculated for $[C_{14}H_{18}O_3]$: 235.1334 $[M+H]^+$, found 235.1335

Heck-type protocol for benzylacetone derivatives [6]



4-(4-Bromophenyl)butan-2-one (15)

Notebook: DJL-7-068, PTS-1-049



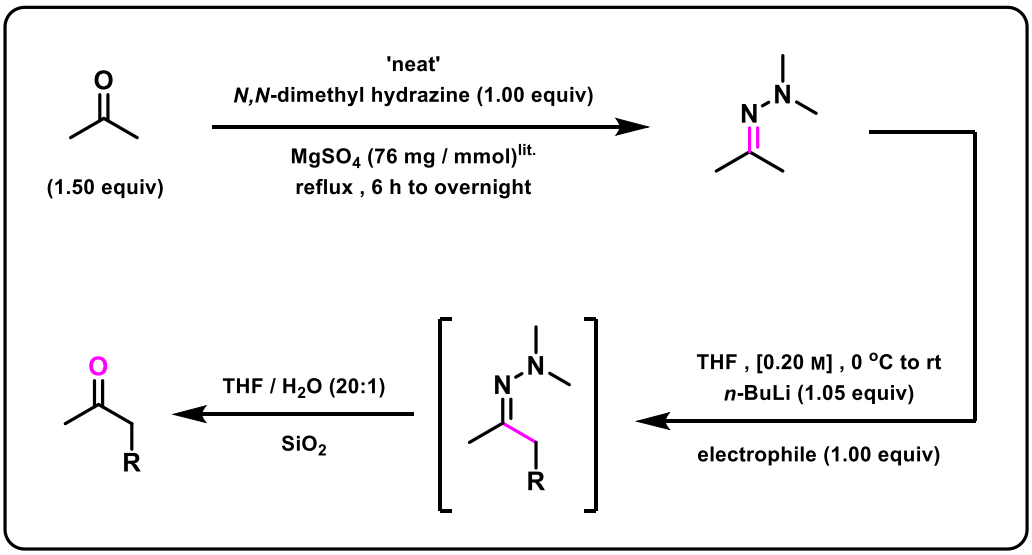
To a RBF charged with $Pd(OAc)_2$ (5 mol %), benzyltriethylammonium chloride (10 mol %), and sodium bicarbonate (2.50 equiv) was added DI water, [0.25 M], and the mixture was stirred at rt 5-10 min. Then 4-iodobromobenzene (1.00 equiv) and 3-buten-2-ol (1.50 equiv) were introduced, the RBF was fitted with an air condenser, under a positive flow of argon, and the reaction was heated to 80 ^{o}C with stirring overnight (~12-16 h). The crude reaction mixture was diluted with ether, transferred to a separatory funnel and extracted with ether (x 2); the combined organic layers were then washed with aqueous brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was subsequently purified by column chromatography on silica gel, eluting with 15% then 25% (ether : hexanes), to afford the desired compound as a faint yellow oil, 35-54%.

TLC: R_f = 0.19 (20% ether : hexanes), UV, I_2, vanillin stain (crimson/maroon spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.44 – 7.33 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.13 (s, 3H)

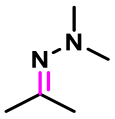
^{13}C NMR: (126 MHz, $CDCl_3$) δ 207.5, 140.1, 131.7, 130.2, 120.0, 45.0, 30.2, 29.2

N,N-Dimethyl hydrazine protocol [7]



1,1-Dimethyl-2-(propan-2-ylidene)hydrazine

Notebook: DJL-7-185/186/189



To an oven dried RBF, charged with a stir bar, were sequentially introduced dry acetone (1.50 equiv) and *N,N*-dimethylhydrazine (50.00 mmol, 1.00 equiv), followed by the addition of anhydrous $MgSO_4$ (1.05 equiv); the resulting slurry was heated to reflux (~6-10 h). Upon completion (*via* crude NMR analysis) the reaction mixture was cooled to rt and directly

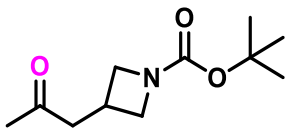
filtered. The excess acetone was removed under reduced pressure to afford a clear colorless oil which, after storage under high vacuum at rt overnight, was of suitable purity to use in subsequent steps; 89-93%.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 2.41 (s, 6H), 1.95 (s, 3H), 1.91 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 165.0, 47.2, 25.3, 18.2

***tert*-Butyl 3-(2-oxopropyl)azetidine-1-carboxylate (16)**

Notebook: DJL-7-188



To a solution of 1,1-dimethyl-2-(propan-2-ylidene)hydrazine (5.00 mmol, 1.00 equiv) in THF [0.20 M] at 0 °C was added *n*-BuLi (1.05 equiv) dropwise, and this mixture was allowed to stir for 1 h, while gradually reaching rt (white precipitate may form initially). The mixture was then, again, brought to 0 °C and a concentrated solution of the alkyl iodide (1.00 equiv, ~[1.00 M] in THF) was transferred to the lithiated solution in a dropwise manner. The reaction was then allowed to stir overnight, thus 0 °C to rt, at which point TLC analysis (Step I, see below) showed full conversion of starting materials. The reaction was then quenched with dilute aqueous ammonium chloride and transferred to a separatory funnel with ether. The aqueous layer was extracted (x 2-3) with ether, the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *via* rotary evaporation to provide the crude *N*,*N*-dimethylhydrazine adduct. The crude material was directly re-dissolved in a THF / water

mixture (~20:1), to which was added silica gel (~1g / mmol). The resulting slurry was stirred at ambient temperature overnight (~12-16 h), at which point TLC analysis indicated complete hydrolysis of the hydrazine (Step II, see below). Stirring was then discontinued and the reaction mixture was allowed to settle, after which the contents were filtered directly (filter cake washed x 2 with ether) and transferred to a separatoy funnel. Extraction from DI water with ether, drying of the combined organic extracts with anhydrous sodium sulfate, filtering off inorganic salts and concentration *via* rotary evaporation provided the crude ketone, which was subsequently purified by column chromatography on silica gel, eluting with 25% then 50% (ether : DCM), to afford the desired compound as a clear colorless oil, 394 mg, 37%.

Step I: TLC: R_f = 0.36 (40% ether : DCM), (TLC developed twice), UV, I_2, vanillin stain (orange spot), some of the ultimately desired ketone was observed on the first TLC, presumably due to *in situ* deprotection of the silica gel TLC plate.

Step II: TLC: R_f = 0.45 (40% ether : DCM), UV, I_2, vanillin stain (lavender spot)

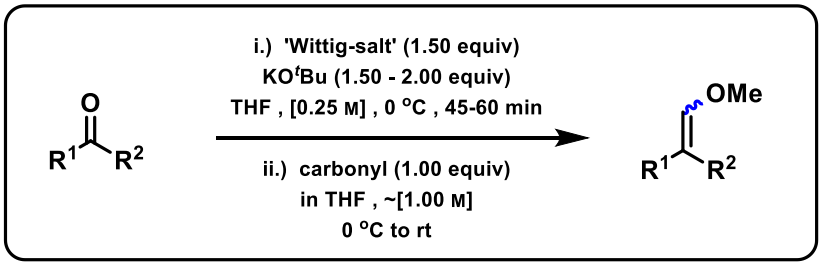
^{1}H NMR: (500 MHz, $CDCl_3$) δ 4.08 (t, *J* = 8.5 Hz, 2H), 3.50 (dd, *J* = 8.8, 5.3 Hz, 2H), 2.85 (m, 1H), 2.77 (m, 2H), 2.13 (s, 3H), 1.41 (s, 9H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 206.9, 156.4, 79.4, 54.6, 48.1, 30.2, 28.5, 24.3

IR: 2979, 2890, 1695, 1399, 1367, 1139, 1035 cm^{-1}

HRMS: (ESI) calculated for $[C_{11}H_{19}NO_3]$: 236.1263 $[M+Na]^+$, found 236.1271

General procedure: Synthesis of substrates *via* Wittig olefination

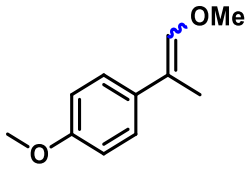


To a flame dried RBF, charged with a magnetic stir bar and the corresponding 'Wittig salt' [(methoxymethyl)triphenylphosphonium chloride, for most cases (1.50 equiv)], was added anhydrous THF, ~[0.25 M], the flask was then cooled to 0 °C in an ice bath with stirring. Potassium *tert*-butoxide (1.50-2.00 equiv), dissolved in dry THF (1 mL x 1 mmol), was then introduced dropwise *via* syringe (the solution becomes instantly vibrant with yellow-orange-red coloration, dependent upon substrate and salt used). The resulting solution was stirred at 0 °C for 45 min, at which time the appropriate ketone (1.00 equiv) was added dropwise *via* syringe (liquid ketones were added directly as 'neat' oils, whereas solid ketones were first dissolved in THF, 1 mL x 1 mmol and transferred as a solution). The mixture was further stirred at 0 °C for 45 min and then was warmed gradually to rt and allowed to stir overnight. After this time TLC analysis showed the formation of a principal product. The mixture was directly concentrated *via* rotatory evaporation and to the viscous crude residue was added cool ether, this suspension was then filtered through a short plug of silica gel with ether to help remove the solid residues of triphenylphosphine oxide. Organics were removed *in vacuo* and the crude material was subsequently purified *via* column chromatography on silica gel to afford the desired compounds as inseparable mixtures of *Z*/*E* isomers.

Note: Alternatively, NaHMDS or KHMDS can be utilized as the base for the preparation of Wittig derived olefins.

1-Methoxy-4-(1-methoxyprop-1-en-2-yl)benzene [8]

Notebook: DJL-7-057



Prepared according to the general 'Wittig' procedure above, 5.00 mmol scale.

Purification: column chromatography on silica gel, eluting with 10% (ether : hexanes), clear viscous oil, 658 mg, 76%. The product was isolated as a 1.25:1 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer.

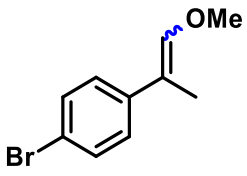
TLC: R_f = 0.46 (20% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.60 – 7.50 (m, 1H), 7.27 – 7.21 (m, 1H), 6.91 – 6.81 (m, 2H), 6.33 (s, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 1.98 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.2, 157.9, 144.2, 143.7, 133.3, 131.1, 128.7, 126.2, 114.3, 113.9, 113.5, 110.5, 60.1, 59.9, 55.4, 55.4, 18.5, 12.9

1-Bromo-4-(1-methoxyprop-1-en-2-yl)benzene

Notebook: PTS-1-056-2



Prepared according to the general 'Wittig' procedure above, 10.0 mmol scale.

Purification: column chromatography on silica gel, eluting with 5% (ether : hexanes), clear oil/ low melting solid, 1.390 g, 61%. The product was isolated as a 1.2:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer.

TLC: R_f = 0.32 (10% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.42 – 7.19 (m, 3H), 7.00 (m, 1H), 6.25(s, 1H), 3.53 (s, 3H), 1.76 (s, 3H)

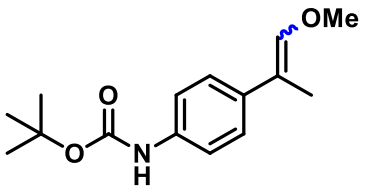
^{13}C NMR: (126 MHz, $CDCl_3$) δ 145.6, 145.4, 139.7, 137.3, 131.5, 131.1, 129.3, 126.6, 119.7, 109.8, 60.4, 60.1, 18.2, 12.5

IR: 2932, 2833, 1653, 1487, 1227, 1134 1082, 1009, 816 cm^{-1}

HRMS: (ESI) calculated for [$C_{10}H_{11}BrO$]: 225.9993 $[M]^+$, found 225.9996

***tert*-Butyl (4-(1-methoxyprop-1-en-2-yl)phenyl)carbamate**

Notebook: PTS-1-050-2



Prepared according to the general 'Wittig' procedure above, 5.00 mmol scale.

Purification: column chromatography on silica gel, eluting with 20% (ether : hexanes), white solid, 562 mg, 43%. The product was isolated as a 1.6:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 1H), 7.28 (m, 2H), 7.24 – 7.20 (m, 1H), 6.44 (bs, 1H), 6.36 (s, 1H), 3.70 (s, 3H), 1.95 (d, J = 1.5 Hz, 3H), 1.52 (s, 9H)

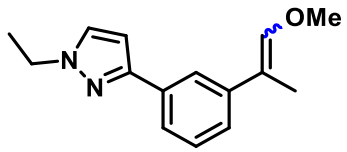
^{13}C NMR: (126 MHz, $CDCl_3$) δ 144.6, 144.2, 136.4, 136.3, 135.7, 133.4, 128.2, 125.6, 118.8, 118.1, 114.2, 110.4, 60.2, 60.0, 28.5, 18.4, 12.7

IR: 3369, 2984, 2932, 2875, 1695, 1529, 1508, 1227, 1149 cm^{-1}

HRMS: (ESI) calculated for [$C_{15}H_{21}NO_3$]: 286.1419 $[M+Na]^+$, found 286.1408

1-Ethyl-3-(3-(1-methoxyprop-1-en-2-yl)phenyl)-1*H*-pyrazole

Notebook: PTS-1-078-2



Prepared according to the general 'Wittig' procedure above, 2.50 mmol scale.

Purification: column chromatography on silica gel, eluting with 50% (ether : hexanes), clear faintly yellow oil, 209 mg, 39%. The product was isolated as a 1.5:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer.

TLC: R_f = 0.49 (50% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.54 (m, 1H), 7.42 – 7.33 (m, 2H), 7.31 (m, 1H), 7.22 – 7.18 (m, 1H), 6.47 (q, *J* = 1.4 Hz, 1H), 6.27 (t, *J* = 1.9 Hz, 1H), 4.18 (m, 2H), 3.74 (s, 3H), 2.01 (d, *J* = 1.4 Hz, 3H) 1.43 (m, 3H)

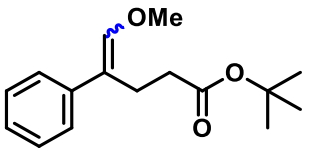
^{13}C NMR: (126 MHz, $CDCl_3$) δ 145.9, 145.5, 143.7, 143.4, 141.3, 138.8, 138.7, 131.2, 130.6, 128.7, 128.4, 128.3, 127.4, 126.6, 126.4, 125.6, 125.1, 113.9, 110.1, 106.1, 106.0, 60.4, 60.2, 44.6, 44.5, 18.3, 16.0, 12.6

IR: 2979, 2932, 2833, 1653, 1456, 1232, 1139 cm^{-1}

HRMS: (ESI) calculated for $[C_{15}H_{18}N_2O]$: 243.1497 $[M+H]^+$, found 243.1498

***tert*-Butyl 5-methoxy-4-phenylpent-4-enoate**

Notebook: PTS-1-047-2



Prepared according to the general 'Wittig' procedure above, 5.0 mmol scale.

Purification: column chromatography on silica gel, eluting with 10% (ether : hexanes), as a light yellow oil, 897 mg, 68%. The product was isolated as a 1.05:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer.

^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 1H), 7.34 – 7.23 (m, 3H), 7.17 (m, 1H), 6.27 (s, 1H), 3.65 (s, 3H), 2.81 – 2.76 (m, 1H), 2.60 – 2.54 (m, 1H), 2.31 – 2.22 (m, 2H), 1.41 (s, 9H)

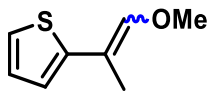
^{13}C NMR: (151 MHz, $CDCl_3$) δ 172.9, 172.8, 146.0, 144.9, 139.3, 136.9, 128.6, 128.3, 128.2, 126.5, 126.3, 126.1, 118.4, 115.2, 80.3, 80.1, 60.2, 60.1, 35.4, 34.4, 28.4, 28.3, 28.2, 22.9

IR: 2979, 2937, 2844, 1726, 1648, 1139 cm^{-1}

HRMS: (ESI) calculated for $[C_{16}H_{22}O_3]$: 262.1569 $[M]^+$, found 262.1573

2-(1-Methoxyprop-1-en-2-yl)thiophene

Notebook: PTS-1-052-1



Prepared according to the general 'Wittig' procedure above, 5.0 mmol scale.

Purification: column chromatography on silica gel, eluting with 10% (ether : hexanes), clear colorless oil, 375 mg, 49%. The product was isolated as a 1.3:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer.

***Note:** Material should be stored under argon protected from light below rt, ~4 ^{o}C.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.26 – 7.04 (m, 1H), 7.04 – 6.98 (m, 1H), 6.96 – 6.84 (m, 1H), 6.33 (q, *J* = 2.8 Hz, 1H), 3.78 (s, 3H), 2.00 (d, *J* = 1.5 Hz, 3H)

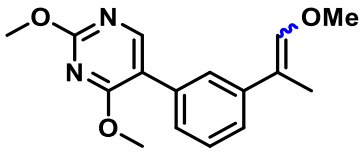
^{13}C NMR: (126 MHz, $CDCl_3$) δ 144.6, 143.5, 141.0, 127.3, 126.0, 124.2, 123.1, 121.3, 121.2, 110.0, 107.4, 60.2, 17.5, 13.2

IR: 2932, 2833, 1742, 1648, 1237, 1212, 1134, 692 cm^{-1}

HRMS: (ESI) calculated for $[C_8H_{10}SO]$: 155.0531 $[M+H]^+$, found 155.0525

2,4-Dimethoxy-5-(3-(1-methoxyprop-1-en-2-yl)phenyl)pyrimidine

Notebook: PTS-1-072-2



Prepared according to the general 'Wittig' procedure above, 1.93 mmol scale.

Purification: column chromatography on silica gel, eluting with 50% (ether : hexanes), clear light lime green viscous oil, 196 mg, 34%. The product was isolated as a 1.4:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer.

TLC: R_f = 0.19 (20% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.23 (m, 1H), 7.70 – 7.51 (m, 1H), 7.37 – 7.21 (m, 3H), 6.40 (s, 1H), 3.99 (m, 3H), 3.97 (m, 3H), 3.66 (m, 3H), 1.93 (m, 3H)

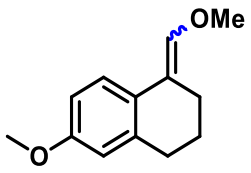
^{13}C NMR: (126 MHz, $CDCl_3$) δ 168.3, 168.3, 164.6, 164.5, 157.7, 157.7, 145.6, 145.1, 145.1, 141.0, 138.7, 133.4, 132.8, 128.5, 128.1, 128.0, 126.9, 126.7, 126.6, 125.6, 124.5, 116.8, 116.6, 114.3, 110.6, 60.3, 60.0, 54.9, 54.9, 54.2, 54.1, 18.3, 12.7

IR: 2942, 2844, 1653, 1596, 1555, 1461, 1383 cm^{-1}

HRMS: (ESI) calculated for [$C_{16}H_{18}N_2O_3$]: 287.1396 $[M+H]^+$, found 287.1403

6-Methoxy-1-(methoxymethylene)-1,2,3,4-tetrahydronaphthalene

Notebook: PTS-1-051-2



Prepared according to the general 'Wittig' procedure above, 5.0 mmol scale.

Purification: column chromatography on silica gel, eluting with 10% (ether : hexanes), as a faint yellow oil, 652 mg, 64%. The product was isolated as a ~5:1mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.35 – 7.13 (m, 1H), 6.66 (m, 1H), 6.58 (m, 1H), 6.51 – 6.42 (m, 1H), 3.74 (m, 3H), 3.66 (m, 3H), 2.67 (t, *J* = 6.3 Hz, 2H), 2.50 – 2.41 (m, 2H), 1.83 – 1.68 (m, 2H)

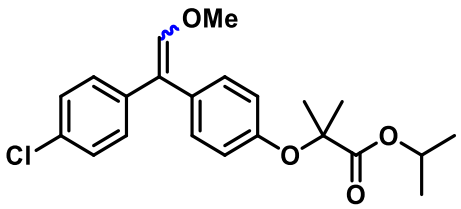
^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.7, 141.4, 138.1, 127.0, 123.0, 114.7, 113.6, 112.6, 103.9, 60.1, 55.4, 31.0, 23.6, 22.7

IR: 2932, 2833, 1648, 1612, 1503, 1217, 1123, 1030 cm^{-1}

HRMS: (ESI) calculated for $[C_{13}H_{16}O_2]$: 205.1228 $[M+H]^+$, found 205.1235

Isopropyl 2-(4-(1-(4-chlorophenyl)-2-methoxyvinyl)phenoxy)-2-methylpropanoate

Notebook: DJL-7-107 & DJL-7-126



Prepared according to the general 'Wittig' procedure above, 7.00 mmol scale.

Purification: column chromatography on silica gel, eluting with 10% then 25% (ether : hexanes), highly viscous light yellow oil, 2.161 g, 80%. The product was isolated as a 1.9:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer. ^{13}C NMR contains doublets for most every peak reflecting close ratio of both isomers.

TLC: R_f = 0.47 (20% ether : hexanes), UV, I_2, vanillin stain (dull orange spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 4H), 7.15 – 7.03 (m, 2H), 6.82 – 6.74 (m, 2H), 6.37 (s, 1H), 5.21 – 4.97 (m, 1H), 3.75 (s, 3H), 1.60 (s, 6H), 1.23 (m, 6H)

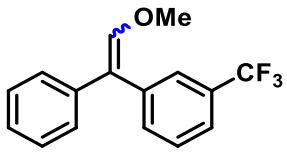
^{13}C NMR: (126 MHz, $CDCl_3$) δ 173.9, 173.8, 154.6, 154.3, 146.2, 146.1, 139.3, 136.3, 133.7, 132.2, 132.1, 131.2, 130.5, 129.7, 129.0, 128.4, 128.2, 119.0, 118.9, 118.5, 79.2, 79.1, 69.0, 69.0, 60.7, 60.7, 25.5, 25.5, 21.7, 21.7

IR: 2979, 2932, 2833, 1726, 1508, 1232, 1097, 832 cm^{-1}

HRMS: (ESI) calculated for [$C_{22}H_{25}ClO_4$]: 388.1441 [M]$^{+}$, found 388.1438

1-(2-Methoxy-1-phenylvinyl)-3-(trifluoromethyl)benzene

Notebook: PTS-1-052-2



Prepared according to the general 'Wittig' procedure above, 5.00 mmol scale.

Purification: column chromatography on silica gel, eluting with 10% (ether : hexanes), colorless oil, 853 mg, 61%. The product was isolated as a 1.4:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer. ^{13}C NMR contains doublets for most every peak reflecting close ratio of both isomers.

***Note:** Product should be stored in the fridge under argon to prevent decomposition.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.71 – 7.24 (m, 8H), 7.20 – 7.17 (m, 1H), 6.49 (s, 1H), 3.79 (s, 3H)

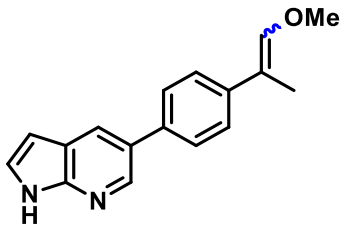
^{13}C NMR: (126 MHz, $CDCl_3$) δ 147.5, 147.4, 141.5, 139.8, 138.6, 137.0, 133.2, 131.7, 131.7, 129.9, 128.8, 128.6, 128.5, 128.4, 128.3, 127.1, 126.9, 126.7, 126.7, 126.6, 124.7, 124.7, 123.3, 123.3, 123.3, 123.2, 123.2, 119.7, 119.4, 60.9, 60.9

IR: 3025, 2937, 2838, 1633, 1326, 1232, 1108, 1076, 697 cm^{-1}

HRMS: (ESI) calculated for $[C_{16}H_{13}F_3O]$: 279.0997 $[M+H]^+$, found 279.1006

5-(4-(1-Methoxyprop-1-en-2-yl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine

Notebook: PTS-1-070-1



Prepared according to the general 'Wittig' procedure above, 2.12 mmol scale.

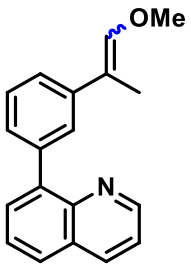
Purification: column chromatography on silica gel, eluting with 30% (EtOAc : hexanes), beige solid, 134 mg, 24%. The product was isolated as a 1.8:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer. ^{13}C NMR contains doublets for most every peak reflecting close ratio of both isomers.

^{1}H NMR: (600 MHz, $CDCl_3$) δ 10.12 (bs, 1H), 8.59 (m, 1H), 8.14 (m, 1H), 7.79 – 7.54 (m, 3H), 7.44 – 7.38 (m, 2H), 6.60 – 6.14 (m, 2H), 3.74 (s, 3H), 2.01 (d, *J* = 1.2 Hz, 3H)

^{13}C NMR: (151 MHz, $CDCl_3$) δ 145.4, 145.1, 142.5, 142.3, 139.5, 137.2, 129.7, 128.2, 127.4, 127.3, 127.2, 127.0, 125.8, 125.7, 125.6, 120.4, 114.1, 105.2, 101.3, 101.3, 60.4, 60.1, 18.4, 12.6

8-(3-(1-Methoxyprop-1-en-2-yl)phenyl)quinoline

Notebook: PTS-1-078-1



Prepared according to the general 'Wittig' procedure above, 2.50 mmol scale.

Purification: column chromatography on silica gel, eluting with 30% (ether : hexanes), highly viscous light bronze oil, 396 mg, 60%. The product was isolated as a 1.5:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer. ^{13}C NMR contains doublets for most every peak reflecting close ratio of both isomers.

TLC: R_f = 0.34 (20% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.96 (m, 1H), 8.20 (m, 1H), 7.88 – 7.81 (m, 1H), 7.75 (m, 1H), 7.71 – 7.58 (m, 2H), 7.56 – 7.51 (m, 1H), 7.50 – 7.27 (m, 3H), 6.32 (q, *J* = 2.8 Hz, 1H), 3.69 (s, 3H), 2.01 (d, *J* = 1.5 Hz, 3H)

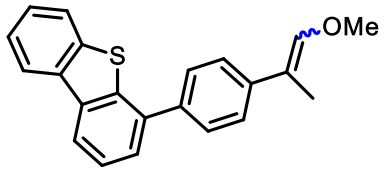
^{13}C NMR: (126 MHz, $CDCl_3$) δ 150.4, 150.3, 146.3, 145.4, 144.7, 141.4, 140.5, 139.7, 139.2, 138.2, 136.3, 136.3, 130.5, 130.4, 129.7, 128.9, 128.8, 128.8, 128.5, 128.0, 127.6, 127.5, 127.4, 127.4, 126.9, 126.4, 126.4, 124.3, 121.1, 121.0, 114.8, 111.2, 60.2, 60.0, 18.5, 12.8

IR: 2922, 2864, 1648, 1601, 1222, 1128, 801 cm^{-1}

HRMS: (ESI) calculated for [$C_{19}H_{17}NO$]: 276.1388 $[M+H]^+$, found 276.1383

4-(4-(1-Methoxyprop-1-en-2-yl)phenyl)dibenzo[*b,d*]thiophene

Notebook: PTS-1-077-2



Prepared according to the general 'Wittig' procedure above, 2.50 mmol scale.

Purification: column chromatography on silica gel, eluting with 10% (ether : hexanes), light beige/ off-white solid, 307 mg, 37%. The product was isolated as a 1.5:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer. ^{13}C NMR contains doublets for most every peak reflecting close ratio of both isomers.

TLC: R_f = 0.62 (20% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.22 – 8.12 (m, 2H), 7.95 – 7.75 (m, 2H), 7.72 (m, 2H), 7.57 – 7.45 (m, 5H), 6.39 (s, 1H), 3.84 – 3.69 (s, 3H), 2.04 (s, 3H)

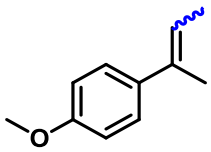
^{13}C NMR: (126 MHz, $CDCl_3$) δ 145.8, 145.4, 140.5, 139.8, 139.8, 138.6, 138.2, 138.2, 137.2, 137.0, 136.4, 136.0, 128.3, 128.0, 127.9, 127.0, 126.9, 126.9, 125.3, 125.2, 125.2, 124.5, 124.4, 122.8, 121.9, 121.8, 120.4, 120.4, 114.2, 60.4, 60.2, 18.4, 12.6

IR: 2965, 2930, 1648, 1444, 1117, 756 cm^{-1}

HRMS: (ESI) calculated for $[C_{22}H_{18}SO]$: 330.1078 $[M]^+$, found 330.1064

1-(But-2-en-2-yl)-4-methoxybenzene [9]

Notebook: PTS-1-036-2



Prepared according to the general 'Wittig' procedure above using ethyltriphenylphosphonium iodide, 5.00 mmol scale.

Purification: column chromatography on silica gel, eluting with 5% then 10% (ether : hexanes), clear colorless oil, 700 mg, 86%. The product was isolated as a 1.0:5.4 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer.

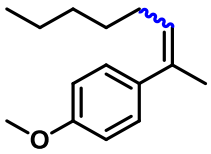
TLC: R_f = 0.82 (20% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.41 – 7.08 (m, 2H), 7.03 – 6.71 (m, 2H), 5.95 – 5.34 (m, 1H), 3.82 (s, 3H), 2.02 (s, 3H), 1.83 – 1.57 (m, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.2, 136.3, 134.3, 129.3, 126.6, 121.3, 121.0, 113.7, 113.6, 55.4, 55.4, 25.6, 15.1

1-Methoxy-4-(oct-2-en-2-yl)benzene [10]

Notebook: PTS-1-038-1



Prepared according to the general 'Wittig' procedure above using hexyltriphenylphosphonium bromide, 5.00 mmol scale.

Purification: column chromatography on silica gel, eluting with 5% then 10% (ether : hexanes), clear colorless oil, 972 mg, 89%. The product was isolated as a 7.8:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer.

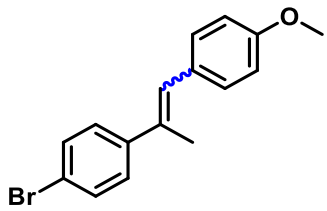
TLC: R_f = 0.71 (20% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.34 – 7.10 (m, 2H), 6.99 – 6.77 (m, 2H), 5.81 – 5.30 (m, 1H), 3.81 (s, 3H), 2.09 – 1.92 (m, 5H), 1.37 – 1.20 (m, 6H), 0.92 – 0.84 (m, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.2, 135.4, 134.7, 129.2, 127.8, 127.4, 126.7, 113.6, 113.5, 55.4, 31.7, 30.1, 29.3, 25.8, 22.7, 14.2

1-Bromo-4-(1-(4-methoxyphenyl)prop-1-en-2-yl)benzene

Notebook: PTS-1-062-2



Prepared according to the general 'Wittig' procedure above using (4-methoxybenzyl)-triphenylphosphonium chloride, 5.00 mmol scale.

Purification: column chromatography on silica gel, eluting with 5% then 10% (ether : hexanes) white solid, 936 mg, 62%. The product was isolated as a 1.6:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer. ^{13}C NMR contains doublets for most every peak reflecting close ratio of both isomers.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.51 – 7.36 (m, 3H), 7.33 – 7.28 (m, 1H), 7.13 – 7.05 (m, 1H), 6.96 – 6.79 (m, 2H), 6.77 (d, *J* = 1.6 Hz, 1H), 6.70 – 6.65 (m, 1H), 3.82 (s, 3H), 2.21 (s, 3H)

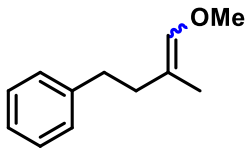
^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.5, 143.2, 135.5, 134.8, 131.8, 131.5, 130.7, 130.5, 130.2, 130.2, 130.0, 130.0, 127.9, 127.7, 126.8, 120.9, 120.8, 113.8, 113.8, 113.6, 55.4, 55.4, 26.8, 17.5

IR: 3015, 2963, 2932, 2838, 1601, 1508, 1248 cm^{-1}

HRMS: (ESI) calculated for [$C_{16}H_{15}BrO$]: 302.0306 $[M]^{+}$, found 302.0298

(4-Methoxy-3-methylbut-3-en-1-yl)benzene

Notebook: DJL-7-213



Prepared according to the general 'Wittig' procedure above, 20.00 mmol scale.

Purification: column chromatography on silica gel, eluting with 1 CV hexanes then 2% (ether : hexanes), clear colorless oil, 3.219 g, 91%. The product was isolated as a 1.5:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer. ^{13}C NMR contains doublets for most every peak reflecting close ratio of both isomers.

TLC: R_f = 0.56 (7% ether : hexanes), UV, I_2, vanillin stain (blue/ purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.38 – 7.23 (m, 3H), 7.20 (m, 2H), 5.77 (s, 1H), 3.50 (m, 3H), 2.74 – 2.68 (m, 2H), 2.43 – 2.17 (m, 2H), 1.63 (d, *J* = 1.5 Hz, 3H)

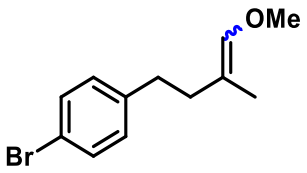
^{13}C NMR: (126 MHz, $CDCl_3$) δ 142.5, 142.5, 142.4, 142.2, 128.6, 128.5, 128.4, 128.3, 125.8, 125.7, 113.9, 113.4, 59.3, 59.3, 36.3, 35.1, 34.0, 30.9, 17.5, 13.0

IR: 2937, 2833, 1679, 1456, 1196, 1123, 702 cm^{-1}

HRMS: (ESI) calculated for [$C_{12}H_{16}O$]: 176.1201 $[M]^+$, found 176.1194

1-Bromo-4-(4-methoxy-3-methylbut-3-en-1-yl)benzene

Notebook: DJL-7-053



Prepared according to the general 'Wittig' procedure above, 3.41 mmol scale.

Purification: column chromatography on silica gel, eluting with 5% (ether : hexanes), pale yellow oil, 566 mg, 65%. The product was isolated as a 1.3:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer. ^{13}C NMR contains doublets for most every peak reflecting close ratio of both isomers.

TLC: R_f = 0.61 (20% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 2H), 7.12 – 7.01 (m, 2H), 5.73 (s, 1H), 3.48 (s, 3H), 2.63 (m, 2H), 2.34 (t, *J* = 8.0 Hz, 1H), 2.16 – 2.12 (t, *J* = 8.0 Hz, 1H), 1.64 (s, 3H)

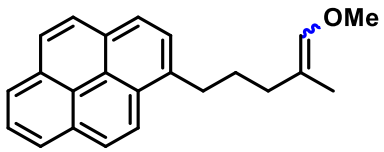
^{13}C NMR: (126 MHz, $CDCl_3$) δ 142.7, 142.4, 141.6, 141.3, 134.0, 133.8, 131.4, 131.3, 130.4, 130.4, 128.8, 128.7, 128.6, 119.6, 119.4, 113.2, 112.9, 59.4, 59.3, 36.1, 34.4, 33.3, 30.6, 17.4, 13.0

IR: 2932, 2838, 1684, 1487, 1206, 1128, 1014 cm^{-1}

HRMS: (ESI) calculated for [$C_{12}H_{15}BrO$]: 254.0306 $[M]^+$, found 254.0308

1-(5-Methoxy-4-methylpent-4-en-1-yl)pyrene

Notebook: DJL-7-141



Prepared according to the general 'Wittig' procedure above, 2.24 mmol scale.

Purification: column chromatography on silica gel, eluting with 1 CV hexanes then 7% (ether : hexanes), white solid, 254 mg, 36%. The product was isolated as a 1.7:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer. ^{13}C NMR contains doublets for most every peak reflecting close ratio of both isomers.

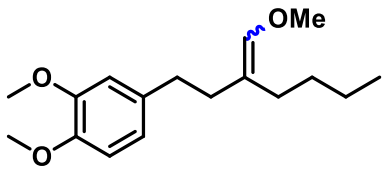
TLC: R_f = 0.52 (20% ether : hexanes), UV

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.30 (m, 1H), 8.16 (m, 2H), 8.14 – 8.09 (m, 2H), 8.06 – 7.97 (m, 3H), 7.89 (m, 1H), 5.94 – 5.74 (s, 1H), 3.58 (s, 3H), 3.33 (m, 2H), 2.21 (t, *J* = 7.5 Hz, 2H), 1.96 (m, 2H), 1.64 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 142.4, 142.3, 137.5, 137.2, 131.6, 131.1, 129.9, 129.8, 128.8, 127.7, 127.7, 127.4, 127.3, 127.2, 126.7, 126.6, 125.9, 125.9, 125.3, 125.2, 125.2, 124.9, 124.9, 124.9, 124.8, 124.7, 123.7, 123.6, 113.9, 113.6, 59.4, 34.1, 33.5, 33.1, 30.2, 29.8, 29.3, 17.4, 12.9

1,2-Dimethoxy-4-(3-(methoxymethylene)heptyl)benzene

Notebook: DJL-7-225



Prepared according to the general 'Wittig' procedure above, 9.60 mmol scale.

Purification: column chromatography on silica gel, eluting with 20% then 40% (ether : hexanes), highly viscous clear colorless oil, 1.253 g, 47%. The product was isolated as a 1.3:1.0 mixture of *Z/E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer. ^{13}C NMR contains doublets for most every peak reflecting close ratio of both isomers.

TLC: R_f = 0.29 (20% ether : hexanes), UV, I_2, vanillin stain (valentines pink spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.84 – 6.64 (m, 3H), 5.75 (s, 1H), 3.88 (d, *J* = 2.5 Hz, 3H), 3.85 (d, *J* = 1.5 Hz, 3H), 3.50 (s, 3H), 2.67 – 2.57 (m, 2H), 2.41 – 2.26 (m, 1H), 2.17 – 2.09 (m, 2H), 1.94 – 1.80 (t, *J* = 7.3 Hz, 1H), 1.40 – 1.26 (m, 4H), 0.90 (m, 3H)

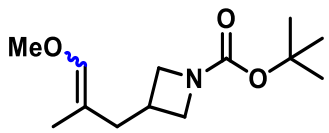
^{13}C NMR: (126 MHz, $CDCl_3$) δ 148.8, 148.8, 147.2, 147.1, 142.7, 142.5, 135.6, 135.2, 120.3, 118.1, 118.1, 111.9, 111.9, 111.3, 111.2, 59.4, 59.4, 56.1, 55.9, 55.9, 34.8, 34.0, 33.8, 31.4, 30.6, 30.2, 29.1, 26.8, 22.8, 22.5, 14.2, 14.1

IR: 2958, 2927, 2849, 1679, 1518, 1461, 1232, 1128, 1035 cm^{-1}

HRMS: (ESI) calculated for $[C_{17}H_{26}O_3]$: 278.1882 $[M]^+$, found 278.1872

***tert*-Butyl 3-(3-methoxy-2-methylallyl)azetidine-1-carboxylate**

Notebook: DJL-7-194



Prepared according to the general 'Wittig' procedure above, using KHMDS as base, 1.34 mmol scale.

Purification: column chromatography on silica gel, eluting with 25% (ether : hexanes), clear colorless oil, 272 mg, 84%. The product was isolated as a 1:1 mixture of *Z*/*E*-stereoisomers, as determined by ^{1}H NMR. The ensuing analytical data corresponds to the major isomer. ^{13}C NMR contains doublets for most every peak reflecting close ratio of both isomers.

TLC: R_f = 0.22 (20% ether : hexanes), UV, I_2, vanillin stain (clay red/ light purple spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.76 (m, 1H), 3.94 (td, *J* = 8.3, 1.4 Hz, 2H), 3.61 – 3.42 (m, 5H), 2.66 – 2.52 (m, 1H), 2.32 (d, *J* = 8.0 Hz, 1H), 2.13 – 2.08 (d, *J* = 8.0 Hz, 1H), 1.49 (m, 3H), 1.42 (s, 9H)

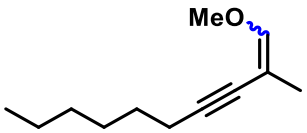
^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.6, 156.6, 143.1, 142.9, 111.3, 111.2, 79.3, 79.1, 59.5, 59.4, 54.4, 39.0, 33.7, 28.6, 28.5, 27.5, 27.2, 17.5, 12.9

IR: 2974, 2932, 2880, 2844, 1700, 1393, 1367, 1134 cm^{-1}

HRMS: (ESI) calculated for $[C_{13}H_{23}NO_3]$: 264.1576 $[M+Na]^+$, found 264.1579

1-Methoxy-2-methyldec-1-en-3-yne

Notebook: PTS-1-056-1



Prepared according to the general 'Wittig' procedure above, 5.00 mmol scale.

Purification: column chromatography on silica gel, eluting with 2% (ether : hexanes), colorless oil, 270 mg, 39%. The product was isolated as predominately the *Z* isomer, as determined by ^{1}H NMR.

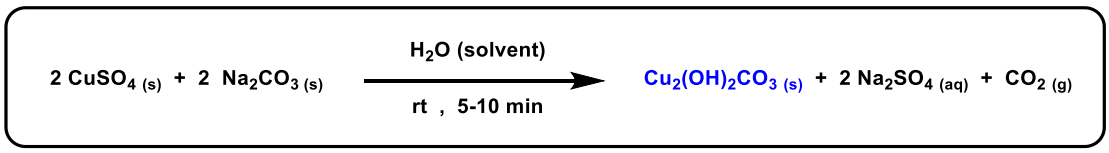
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.52 – 6.04 (s, 1H), 3.63 (m, 3H), 2.27 (m, 2H), 1.69 (m, 3H), 1.55 – 1.48 (m, 2H), 1.41 – 1.26 (m, 6H), 0.89 (m, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 151.8, 97.7, 87.3, 80.5, 60.1, 31.5, 29.2, 28.7, 22.7, 19.6, 14.4, 14.2

IR: 2963, 2927, 2864, 2215, 1679, 1648, 1456, 1227, 1139 cm^{-1}

HRMS: (ESI) calculated for $[C_{12}H_{20}O]$: 181.1592 $[M+H]^+$, found 181.1587

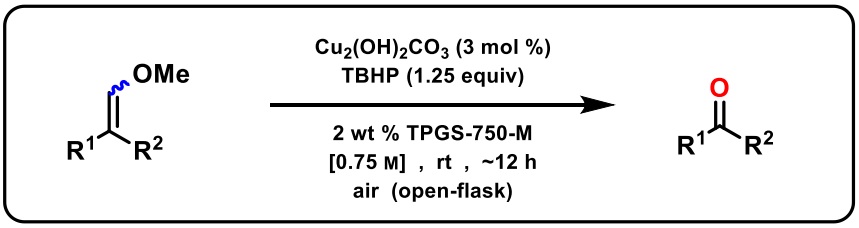
Preparation of basic cupric carbonate [11]



Notebook: DJL-7-083

To an Erlenmeyer flask, vigorously stirring a dilute aqueous solution of sodium carbonate (10.00 mmol), was 'rapidly' introduced a dilute solution of copper sulfate (10.00 mmol) in DI water (instant reaction). This mixture was allowed to vigorously stir at rt for 5-10 min, at which point stirring was discontinued and the contents of the reaction were momentarily allowed to settle (5-10 min). Then, direct transfer of the entire flask was filtered *via* Buchner-funnel (with mild to light vacuum). The filter cake was washed with ice cold DI water (x 2), followed by pentanes (x 2-3) and left under vacuum for ~30 min, and then allowed to air dry overnight. The resulting, free-flowing, verditer-to-mountain blue copper salt was used as such for the following reactions, without need for any further processing, 1.481 g, 67%.

2. Oxidative Cleavage Protocol and Products Characterization:

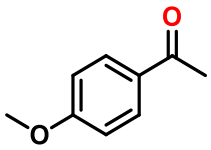


To a screw cap vial, containing a Teflon coated stir bar, were weighed the starting methyl enol ether substrate (1.00 equiv) and basic cupric carbonate (3 mol %, based on copper). The vial was then charged with 2 wt % TPGS-750-M, [0.75 M], and placed on a stir plate with medium to strong stirring. Then *tert*-butyl hydroperoxide (~70% in water, 1.25 equiv) was introduced dropwise and the reaction was allowed to stir (without a cap) open to air for ~ 12 h. Once the reaction was complete, as indicated by TLC analysis, the reaction was diluted with a small volume of EtOAc (or ether), stirred ~5-10 min and filtered through a short plug of silica gel. Volatiles were removed *in vacuo* and the crude residue was subsequently purified by column chromatography of silica gel, to afford the desired compound.

WARNING! *tert*-Butyl hydroperoxide is supplied as ~70% aqueous commercial solution. Reaction mixtures can be potentially explosive if the concentration of peroxide exceeds that of ~85 – 90% in either organic or aqueous solutions. If uncertain of the safety for a given experiment deploy a blast-shield and have a large amount of sand within reach.

1-(4-Methoxyphenyl)ethan-1-one (1)

Notebook: PTS-1-060-1



Prepared according to the general 'Oxidative Cleavage' procedure above, 0.50 mmol scale.

Purification: column chromatography on silica gel, eluting with 5% (ether : hexanes), white solid, 65.0 mg, 87%.

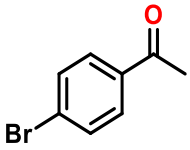
Spectral data were in full agreement with that of the identical commercial grade compound.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.97 – 7.83 (m, 2H), 6.95 – 6.90 (m, 2H), 3.86 (s, 3H), 2.55 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 196.9, 163.6, 130.7, 130.5, 113.8, 55.6, 26.5

1-(4-Bromophenyl)ethan-1-one (2)

Notebook: PTS-1-060-2



Prepared according to the general 'Oxidative Cleavage' procedure above, 0.50 mmol scale.

Purification: column chromatography on silica gel, eluting with 5% (ether : hexanes), white solid, 83.1 mg, 84%.

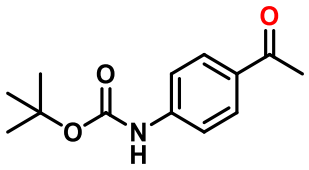
Spectral data were in full agreement with that of the identical commercial grade compound.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.84 – 7.79 (m, 2H), 7.65 – 7.57 (m, 2H), 2.58 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 197.1, 136.0, 132.0, 123.0, 128.4, 26.7

***tert*-Butyl (4-acetylphenyl)carbamate (3)**

Notebook: PTS-1-058-3



Prepared according to the general 'Oxidative Cleavage' procedure above with 10% v/v THF to aid in solubility, 0.50 mmol scale.

Purification: column chromatography on silica gel, eluting with 25% (EtOAc : hexanes), white crystalline solid, 105.2 mg, 89%.

TLC: R_f = 0.49 (50% EtOAc : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.94 – 7.87 (m, 2H), 7.48 – 7.42 (m, 2H), 6.77 (bs, 1H), 2.56 (s, 3H), 1.52 (s, 9H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 197.1, 152.3, 143.1, 132.0, 123.0, 117.5, 81.4, 28.4, 26.5

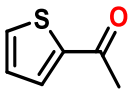
IR: 3245, 3175, 3099, 3006, 2977, 1718, 1665, 1584, 1543, 1240, 1152, 587 cm^{-1}

HRMS: (ESI) calculated for $[C_{13}H_{17}NO_3]$: 236.1287 $[M+H]^+$, found 236.1295

*** Also performed on a 1.00 mmol scale, utilizing the exact 'general procedure' above. White solid, 193 mg, 82%.

1-(Thiophen-2-yl)ethan-1-one (4)

Notebook: PTS-1-057-3



Prepared according to the general 'Oxidative Cleavage' procedure above, 0.50 mmol scale.

Purification: column chromatography on silica gel, eluting with 5% (ether : hexanes), faintly yellow oil, 36.2 mg, 57%.

Spectral data were in full agreement with that of the identical commercial grade compound.

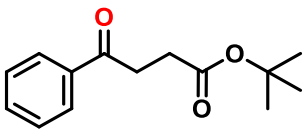
TLC: R_f = 0.31 (5% ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.69 (m, 1H), 7.62 (m, 1H), 7.12 (m, 1H), 2.55 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 190.8, 144.7, 133.9, 132.6, 128.2, 27.0

***tert*-Butyl 4-oxo-4-phenylbutanoate (5)**

Notebook: PTS-1-059-2



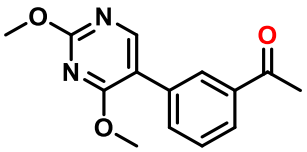
Prepared according to the general ‘Oxidative Cleavage’ procedure above, 0.50 mmol scale.

Purification: column chromatography on silica gel, eluting with 5% (ether : hexanes), clear colorless oil, 89.1 mg, 76%.

*All sprectral data is in agreement with that given above.

1-(3-(2,4-Dimethoxypyrimidin-5-yl)phenyl)ethan-1-one (6)

Notebook: PTS-1-074-2



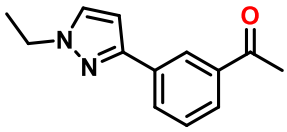
Prepared according to the general ‘Oxidative Cleavage’ procedure above, 0.30 mmol scale.

Purification: column chromatography on silica gel, eluting with 30% (EtOAc : hexanes), beige tan solid, 55.3 mg, 71%.

*All sprectral data is in agreement with that given above.

1-(3-(1-Ethyl-1*H*-pyrazol-3-yl)phenyl)ethan-1-one (7)

Notebook: PTS-1-080-2



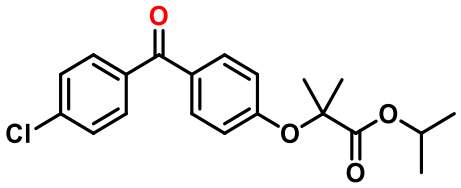
Prepared according to the general ‘Oxidative Cleavage’ procedure above, 0.50 mmol scale.

Purification: column chromatography on silica gel, eluting with 40% (ether : hexanes), light yellow oil, 80.4 mg, 73%.

*All sprectral data is in agreement with that given above.

Isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate (Fenofibrate) (8)

Notebook: DJL-7-146-B



Prepared according to the general 'Oxidative Cleavage' procedure above, 0.20 mmol scale.

Purification: column chromatography on silica gel, eluting with 8% then 15% (ether : hexanes), off-white solid, 65.4 mg, 91%.

TLC: R_f = 0.41 (20% ether : hexanes), UV, I_2, (does not stain with vanillin)

***Starting material R_f value very close, slightly higher, and does stain with vanillin

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.75 – 7.67 (m, 4H), 7.46 – 7.41 (d, *J* = 8.0 Hz, 2H), 6.88 – 6.84 (d, *J* = 9.0 Hz, 2H), 5.08 (p, *J* = 6.2 Hz, 1H), 1.65 (s, 6H), 1.19 (d, *J* = 6.5 Hz, 6H)

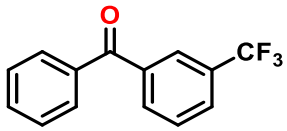
^{13}C NMR: (126 MHz, $CDCl_3$) δ 194.3, 173.2, 159.9, 138.4, 136.6, 132.1, 131.3, 130.3, 128.6, 117.4, 79.5, 69.4, 25.5, 21.6

IR: 2983, 1730, 1654, 1590, 1287, 1147, 1088, 925, 768 cm^{-1}

HRMS: (ESI) calculated for $[C_{20}H_{21}ClO_4]$: 360.1128 $[M]^+$, found 360.1113

Phenyl(3-(trifluoromethyl)phenyl)methanone (9)

Notebook: PTS-1-058-4/5



Prepared according to the general 'Oxidative Cleavage' procedure above, 0.50 mmol scale.

Purification: column chromatography on silica gel, eluting with 5% (ether : hexanes), white crystals, 76-81%.

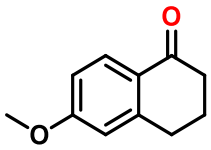
Spectral data were in full agreement with that of the identical commercial grade compound.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.00 – 7.96 (m, 1H), 7.85 (m, 1H), 7.81 – 7.78 (m, 2H), 7.65 – 7.61 (m, 2H), 7.54 – 7.50 (m, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 195.4, 138.4, 136.9, 133.3, 133.2, 130.2, 129.1, 129.0, 129.0, 128.7, 126.9, 126.8

6-Methoxy-3,4-dihydronaphthalen-1(2*H*)-one (10)

Notebook: PTS-1-065-4



Prepared according to the general 'Oxidative Cleavage' procedure above, 0.50 mmol scale.

Purification: column chromatography on silica gel, eluting with 20% then 30% (ether : hexanes), off-white solid, 73.0 mg, 83%.

Spectral data were in full agreement with that of the identical commercial grade compound.

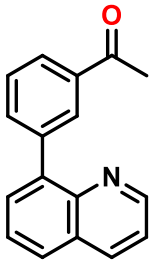
TLC: R_f = 0.14 (10 % ether : hexanes), UV, I_2

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.7 Hz, 1H), 6.81 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.69 (m, 1H), 3.85 (s, 3H), 2.92 (t, *J* = 6.0 Hz, 2H), 2.60 (t, *J* = 6.5 Hz, 2H), 2.13 – 2.08 (m, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 197.3, 163.7, 147.1, 129.8, 126.5, 113.2, 112.7, 55.5, 39.0, 30.3, 23.5

1-(3-(Quinolin-8-yl)phenyl)ethan-1-one (11)

Notebook: PTS-1-080-1



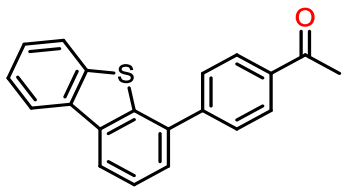
Prepared according to the general 'Oxidative Cleavage' procedure above, 0.50 mmol scale.

Purification: column chromatography on silica gel, eluting with 30% (ether : hexanes), viscous light yellow oil, 98.1 mg, 80%.

*All sprectral data is in agreement with that given above.

1-(4-(Dibenzo[b,d]thiophen-4-yl)phenyl)ethan-1-one (12)

Notebook: PTS-1-079-2



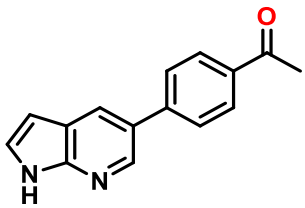
Prepared according to the general 'Oxidative Cleavage' procedure above, 0.50 mmol scale.

Purification: column chromatography on silica gel, eluting with 20% (ether : hexanes), white solid, 66.4 mg, 44%.

*All sprectral data is in agreement with that given above.

1-(4-(1*H*-Pyrrolo[2,3-*b*]pyridin-5-yl)phenyl)ethan-1-one (13)

Notebook: PTS-1-079-3



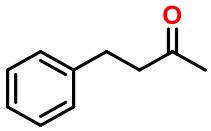
Prepared according to the general 'Oxidative Cleavage' procedure above, 0.13 mmol scale.

Purification: column chromatography on silica gel, eluting with 100% EtOAc, faint beige solid, 19.0 mg, 61%.

*All sprectral data is in agreement with that given above.

4-Phenylbutan-2-one (14)

Notebook: DJL-7-113-B



Prepared according to the general 'Oxidative Cleavage' procedure above, 0.40 mmol scale.

Purification: column chromatography on silica gel, eluting with 20% (ether : hexanes), clear colorless oil, 26.0 mg, 43%.

Spectral data were in full agreement with that of the identical commercial grade compound.

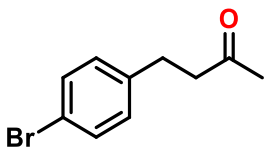
TLC: R_f = 0.27 (20% ether : hexanes), UV, I_2, vanillin stain (violet spot)

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.23 – 7.14 (m, 3H), 2.90 (m, 2H), 2.79 – 2.75 (m, 2H), 2.14 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 208.1, 141.1, 128.6, 128.4, 126.2, 45.3, 30.2, 29.9

4-(4-Bromophenyl)butan-2-one (15)

Notebook: DJL-7-061-A



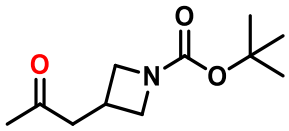
Prepared according to the general 'Oxidative Cleavage' procedure above, 0.40 mmol scale.

Purification: column chromatography on silica gel, eluting with 15% then 25% (ether : hexanes), clear colorless oil, 47.1 mg, 52%.

*All sprectral data is in agreement with that given above.

tert-Butyl 3-(2-oxopropyl)azetidine-1-carboxylate (16)

Notebook: DJL-7-196-B



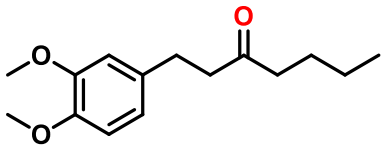
Prepared according to the general 'Oxidative Cleavage' procedure above, 0.40 mmol scale.

Purification: column chromatography on silica gel, eluting with 20% then 50% (ether : DCM), viscous oil, 33.0 mg product, 39%; 31.6 mg recovered starting material, 43%; 69% yield based on recovered starting material.

*All sprectral data is in agreement with that given above.

1-(3,4-Dimethoxyphenyl)heptan-3-one (17)

Notebook: DJL-7-227-C



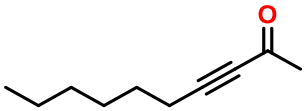
Prepared according to the general 'Oxidative Cleavage' procedure above, 0.30 mmol scale.

Purification: column chromatography on silica gel, eluting with 25% (ether : hexanes), light yellow viscous oil, 40.0 mg, 53%.

*All sprectral data is in agreement with that given above.

Dec-3-yn-2-one (18) [12]

Notebook: PTS-1-065-5



Prepared according to the general 'Oxidative Cleavage' procedure above, 0.50 mmol scale.

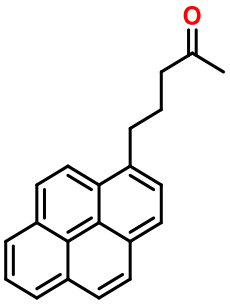
Purification: column chromatography on silica gel, eluting with 10% (ether : hexanes), clear colorless oil, 50.1 mg, 66%.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 2.34 (t, *J* = 7.0 Hz, 2H), 2.31 (s, 3H), 1.58 – 1.53 (m, 2H), 1.39 (m, 2H), 1.32 – 1.26 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$) δ 185.1, 94.3, 81.5, 32.9, 31.3, 28.7, 27.8, 22.6, 19.0, 14.1

5-(Pyren-1-yl)pentan-2-one (19)

Notebook: DJL-7-154-A



Prepared according to the general ‘Oxidative Cleavage’ procedure above, 0.239 mmol scale.

Purification: column chromatography on silica gel, eluting with 40% (ether : hexanes), viscous oil, 39.7 mg, 58%.

*All sprectral data is in agreement with that given above.

3.6. Experimental References

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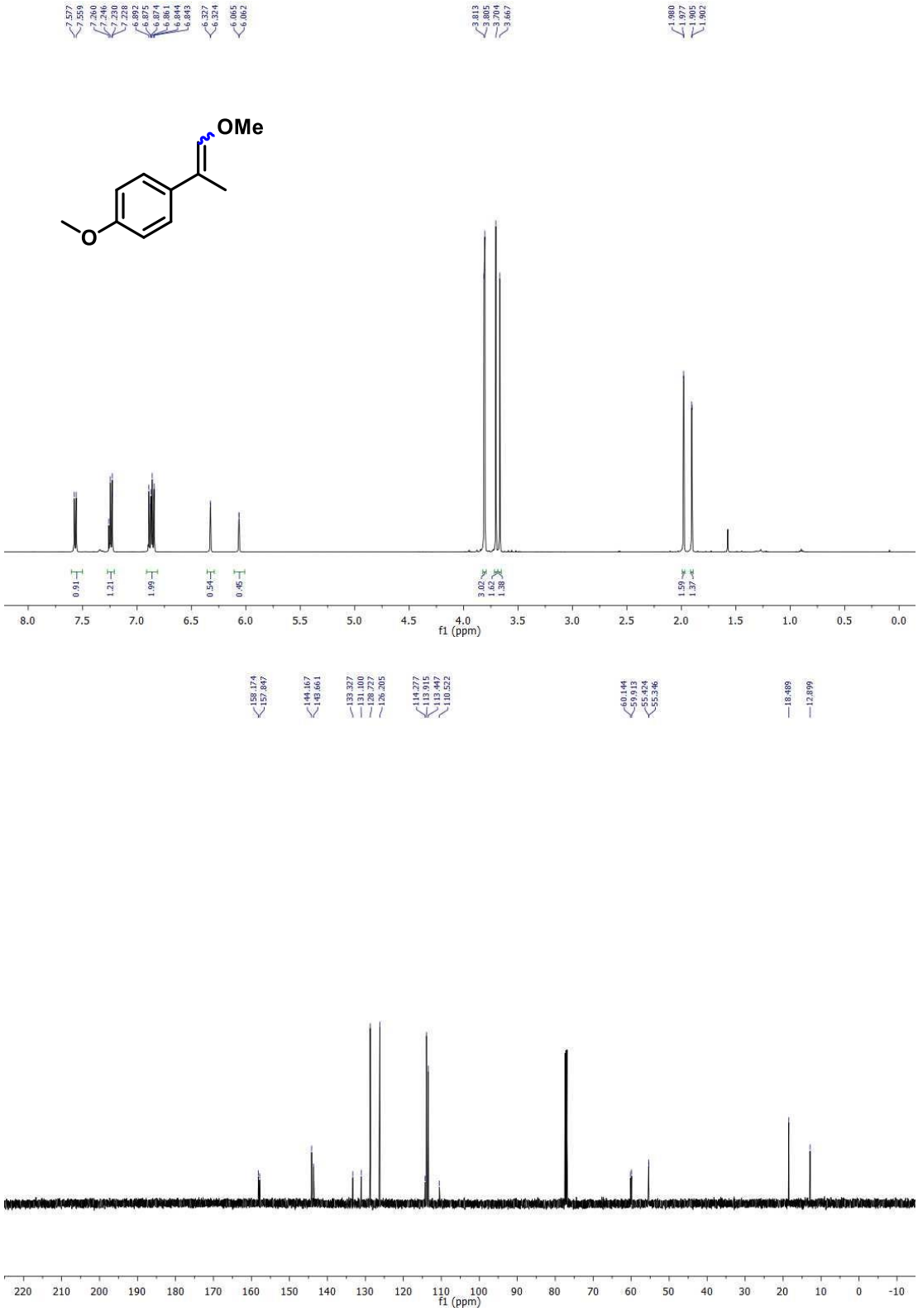
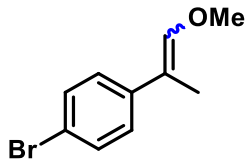
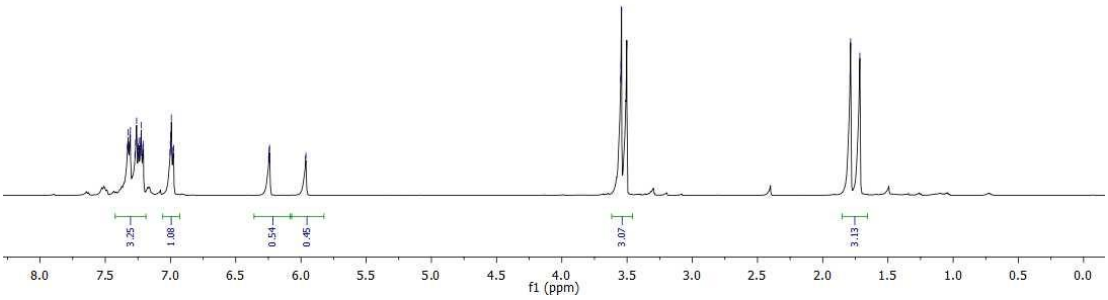
11. Hepburn, J. R. I. *J. Chem. Soc.* **1927**, *0*, 2883.
12. Leung, L. T.; Leung, S. K.; Chiu, P. *Org. Lett.* **2005**, *7*, 5249.

3.7. Spectral Data




OMe
Br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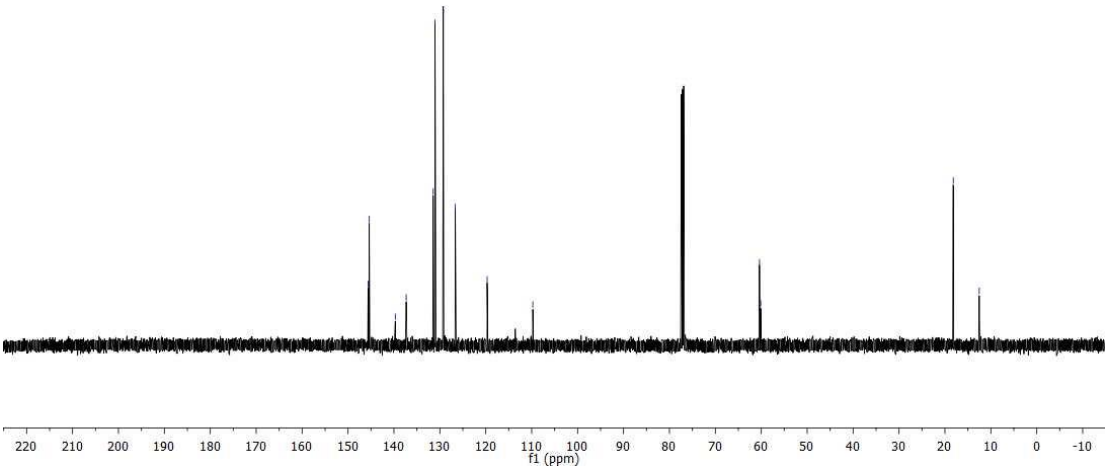
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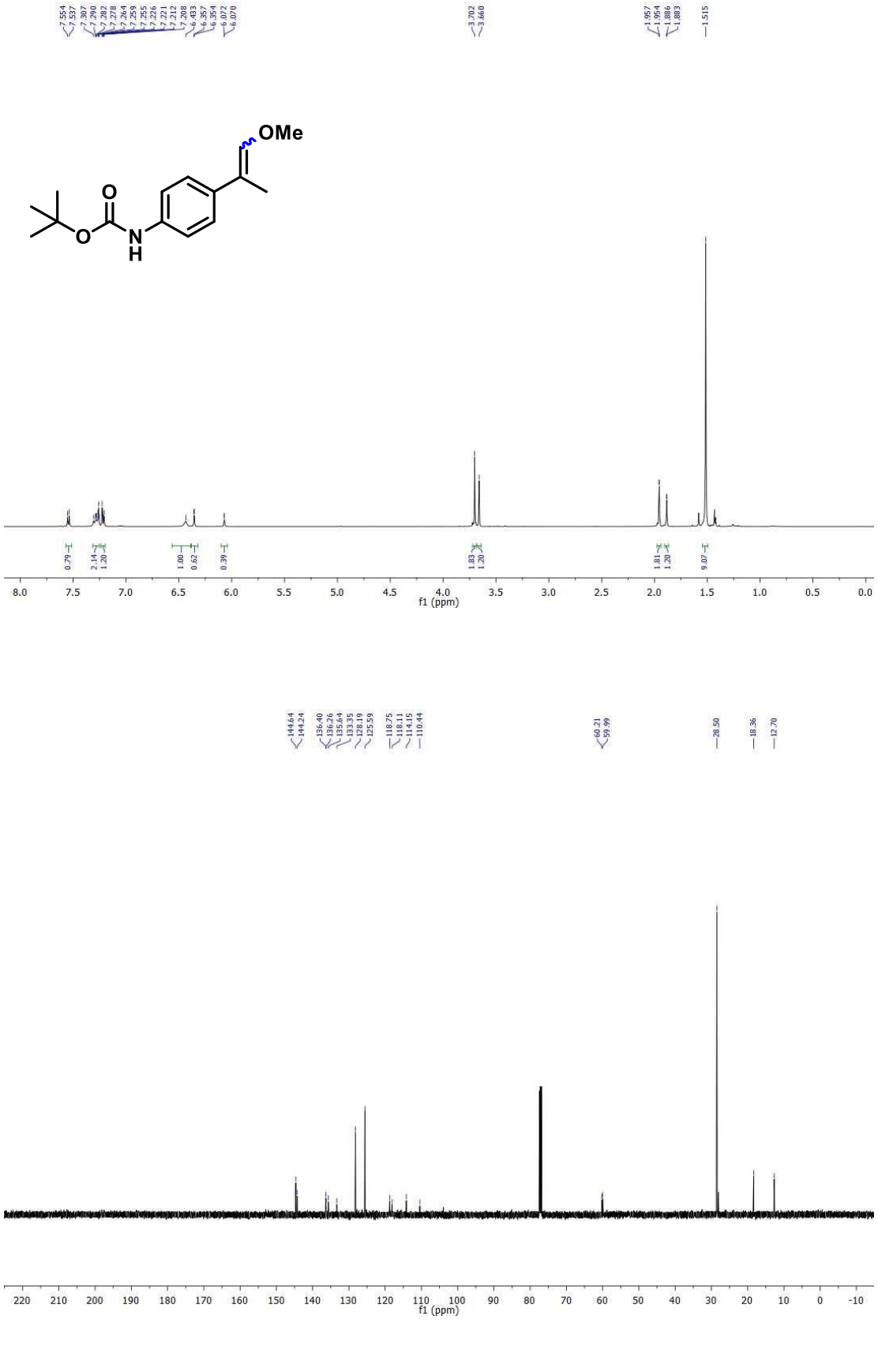
f1 (ppm)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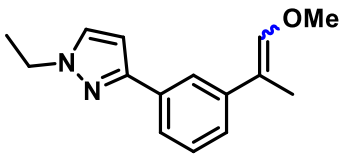
f1 (ppm)
f1 (ppm)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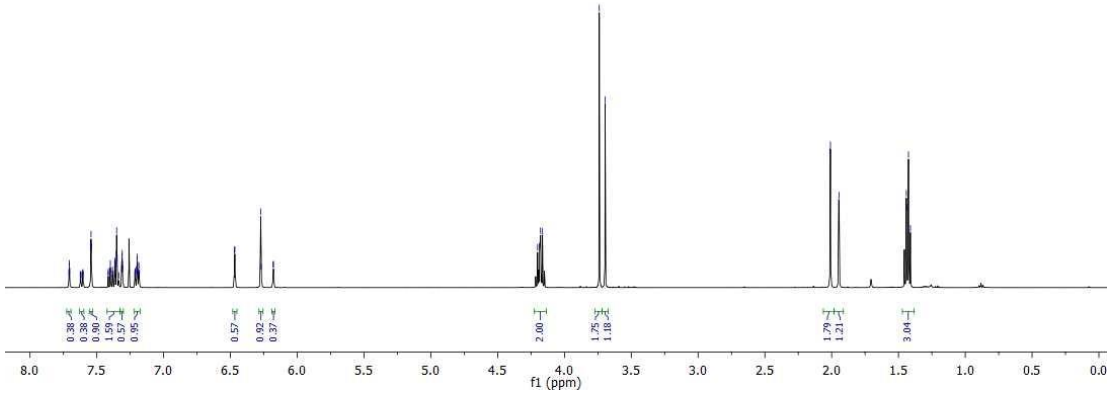
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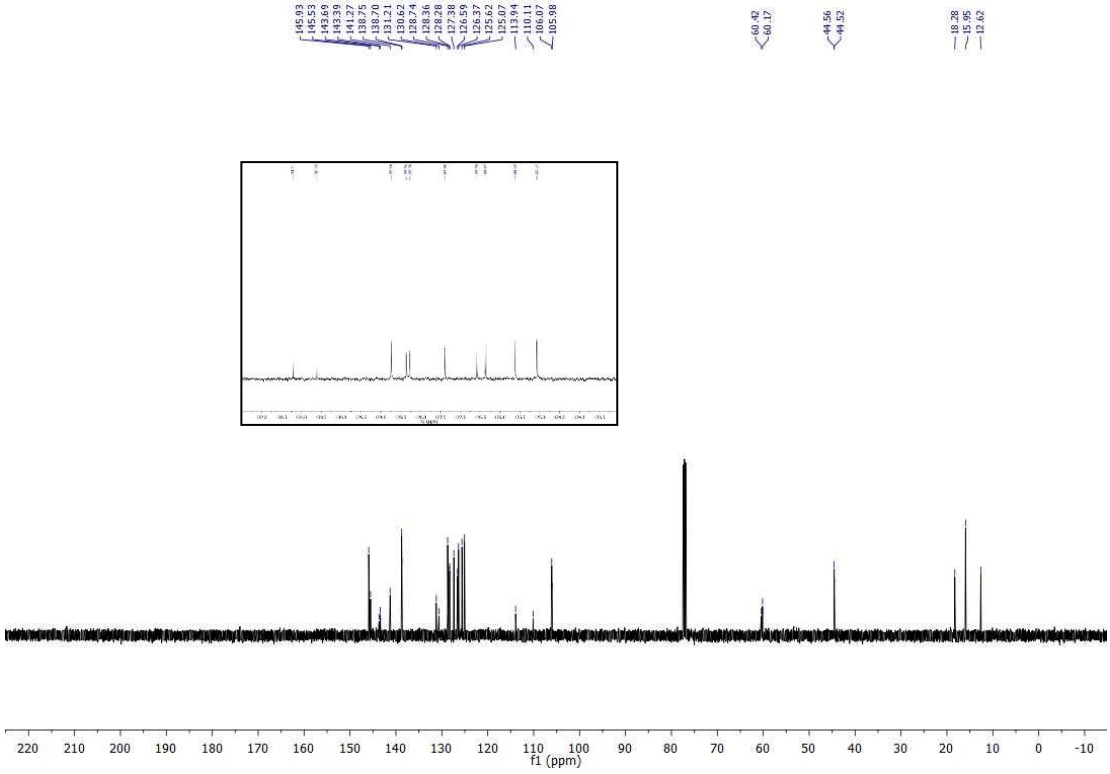
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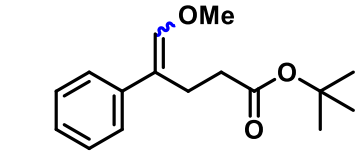
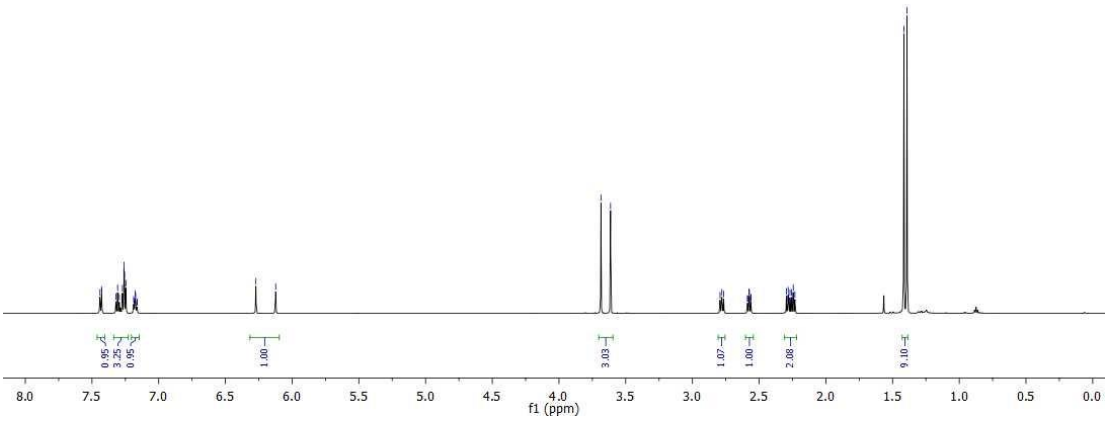

OMe
O
O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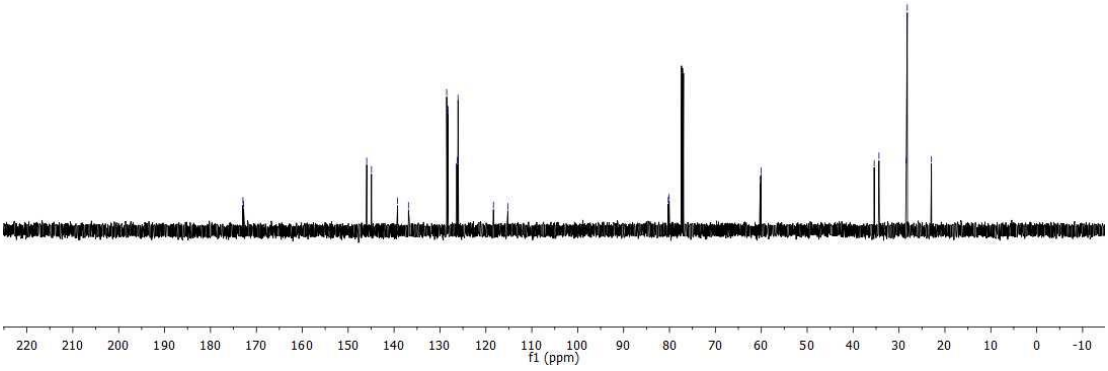
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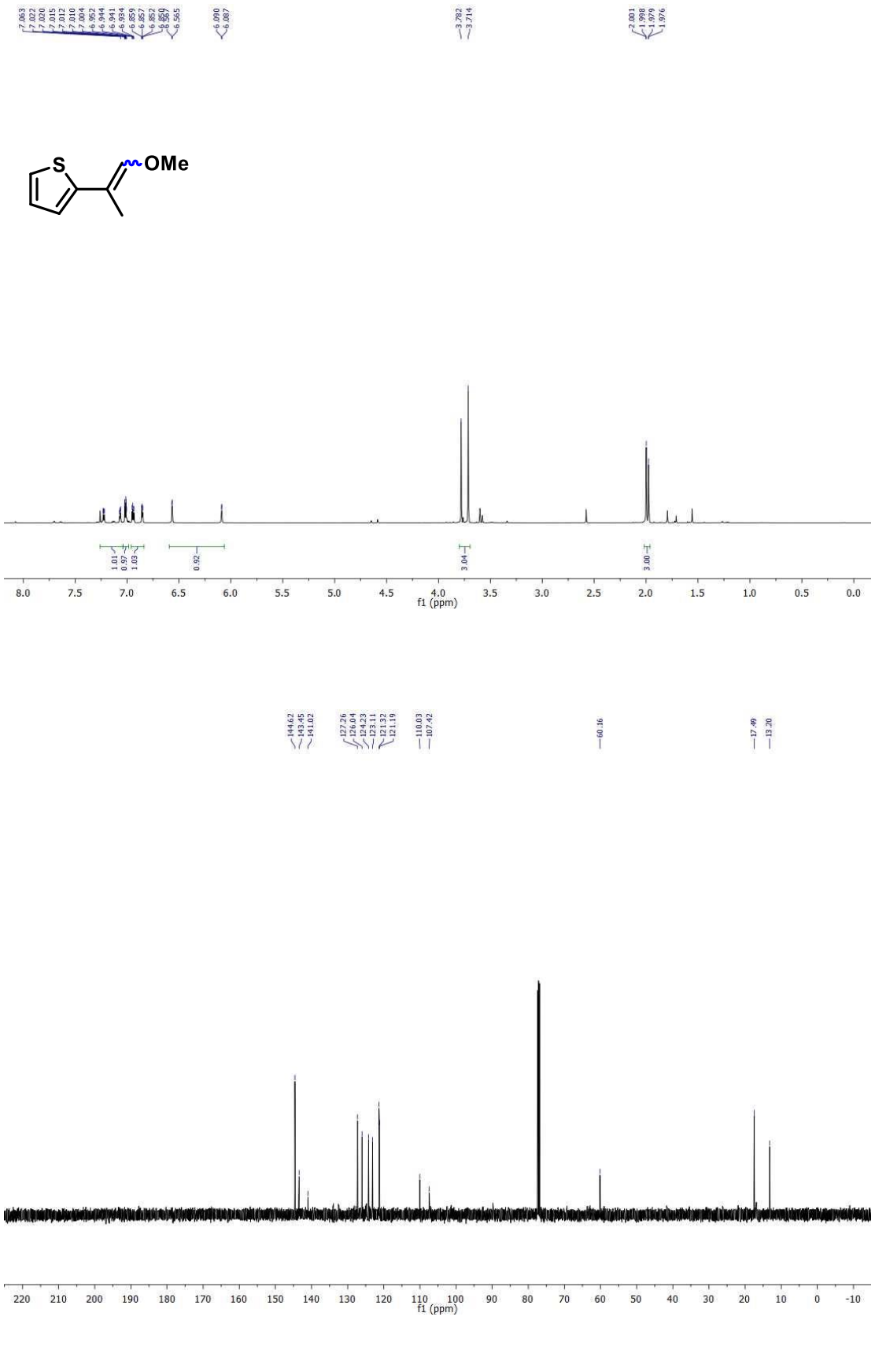
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
144.62
143.45
141.02
127.26
126.04
124.23
123.11
121.32
121.19
110.03
107.42
60.16
17.49
13.20
220
210
200
190
180
170
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100
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40
30
20
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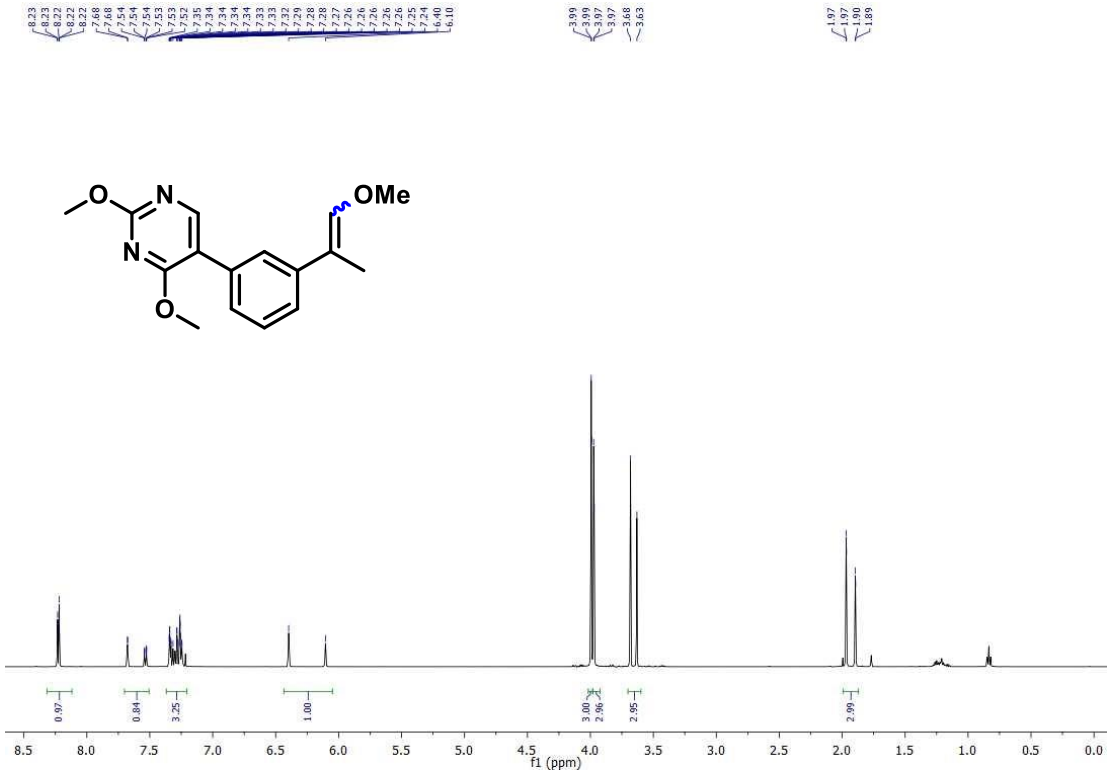
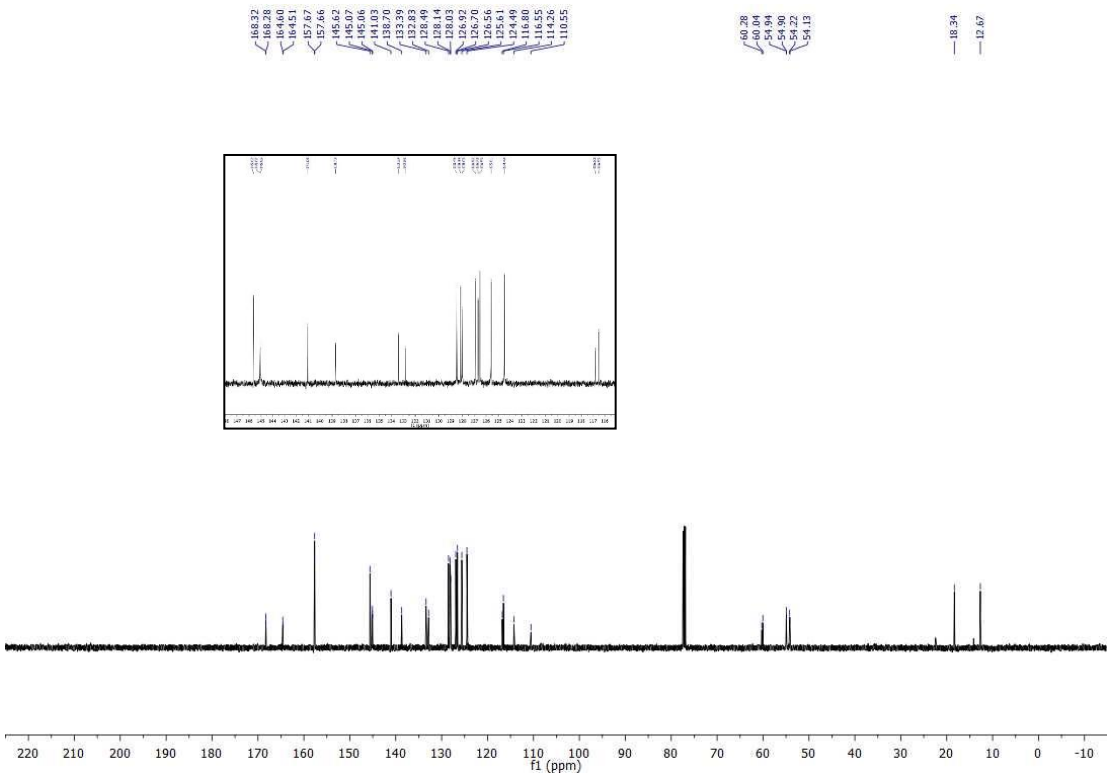
0
-10
f1 (ppm)


OMe
f1 (ppm)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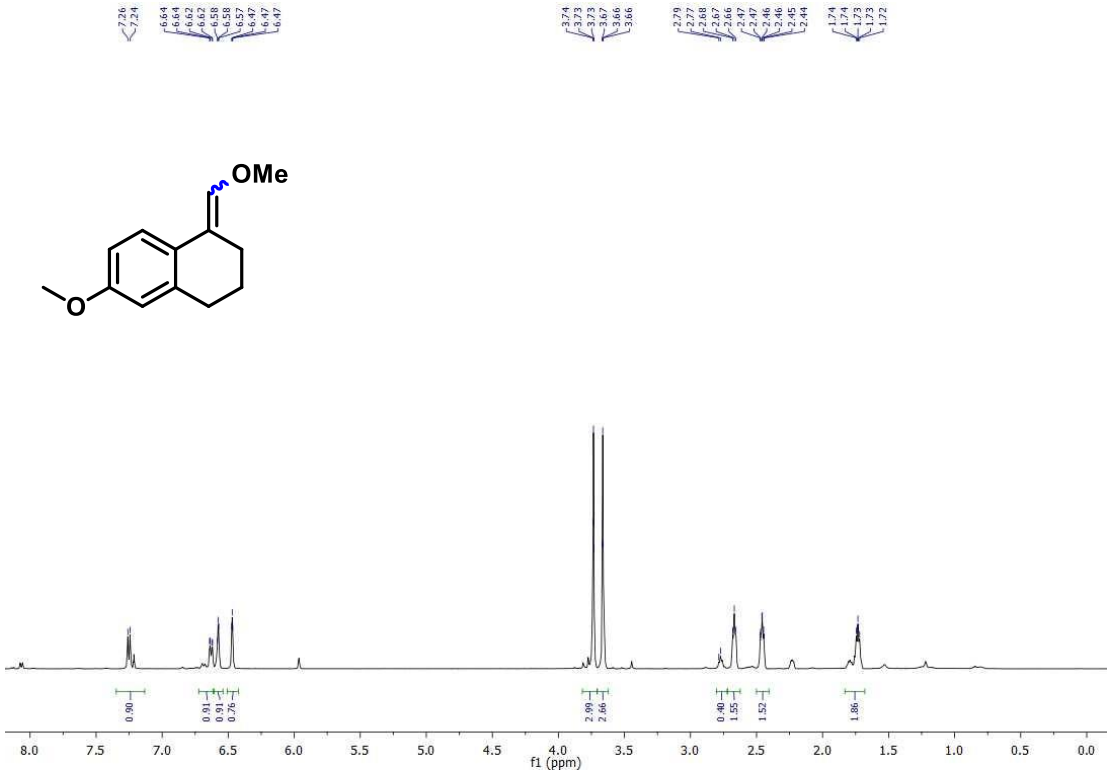
OMe
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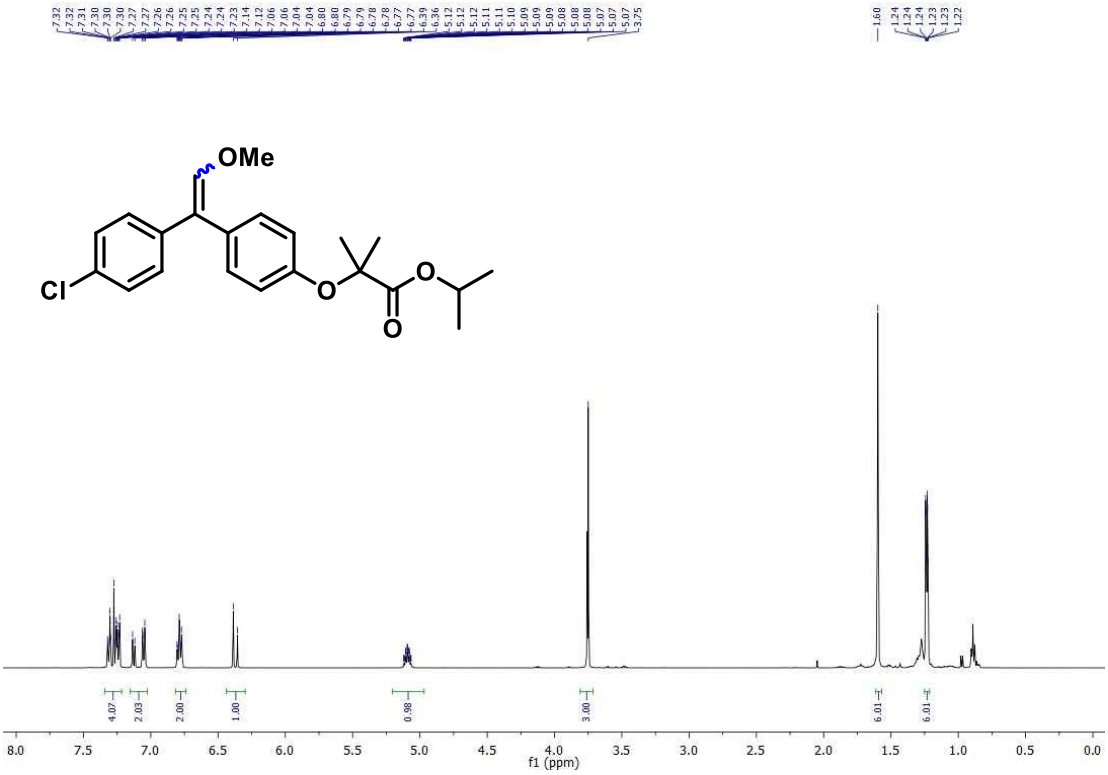
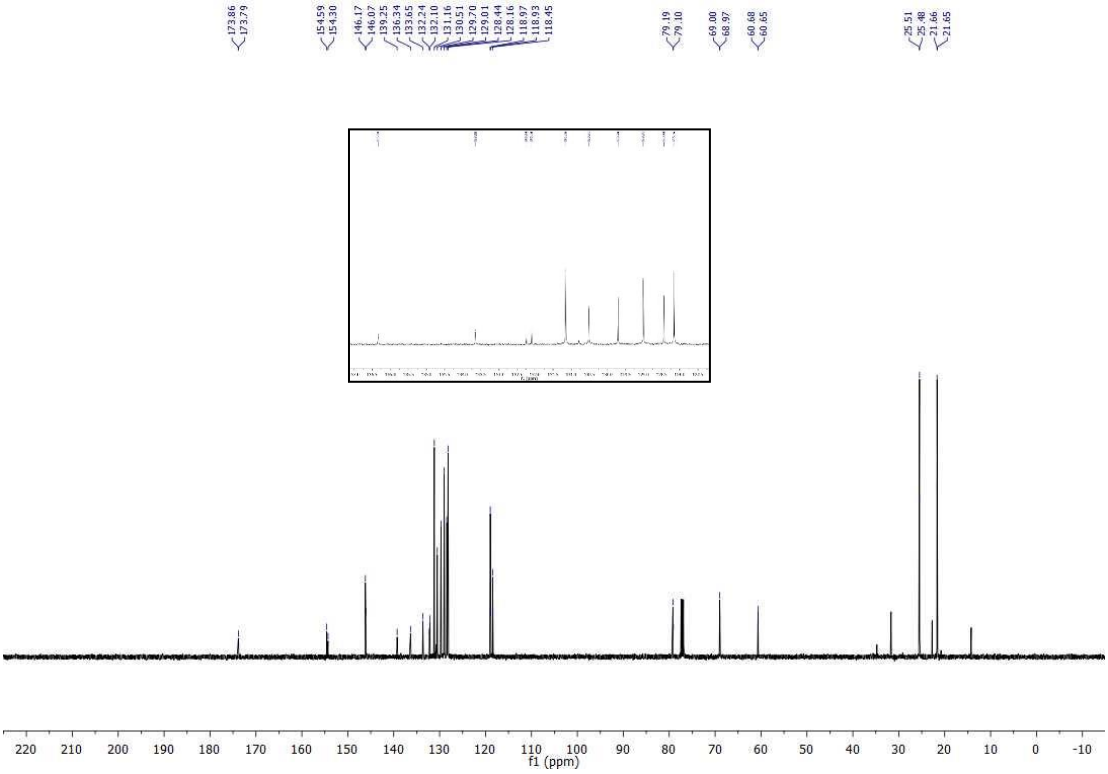
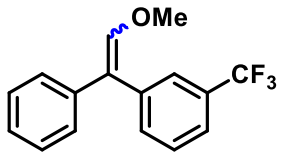
f1 (ppm)


OMe
Cl
O
O
O
f1 (ppm)


f1 (ppm)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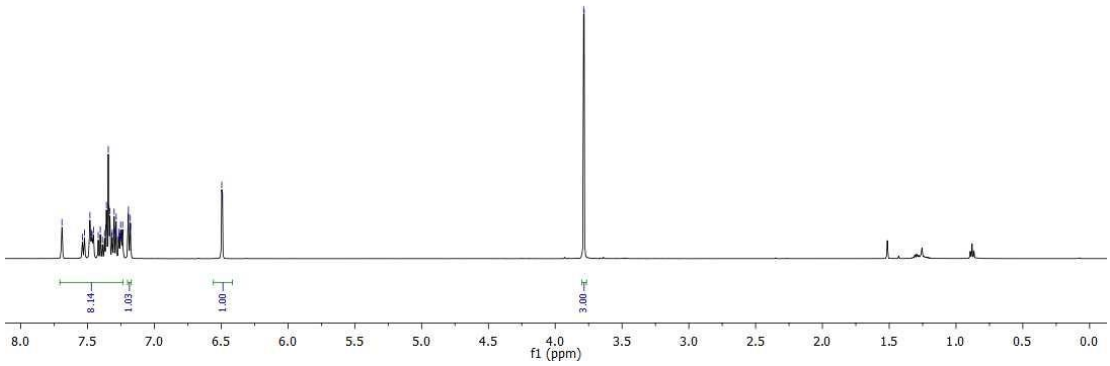
CF3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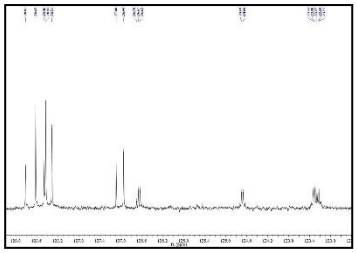
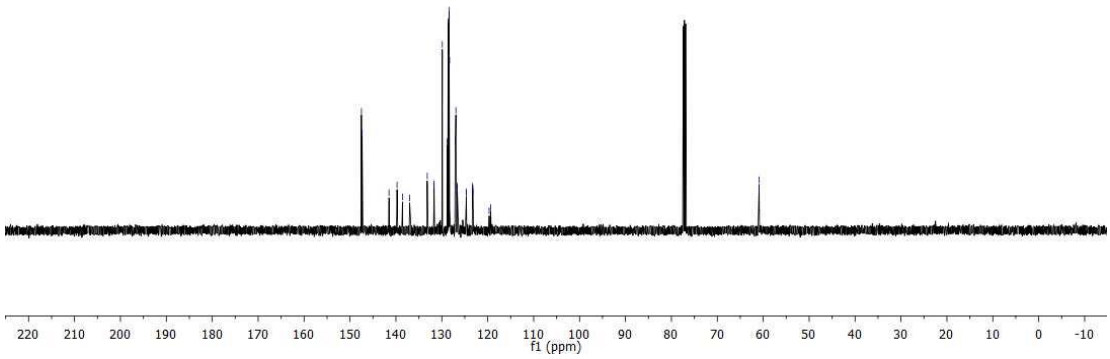
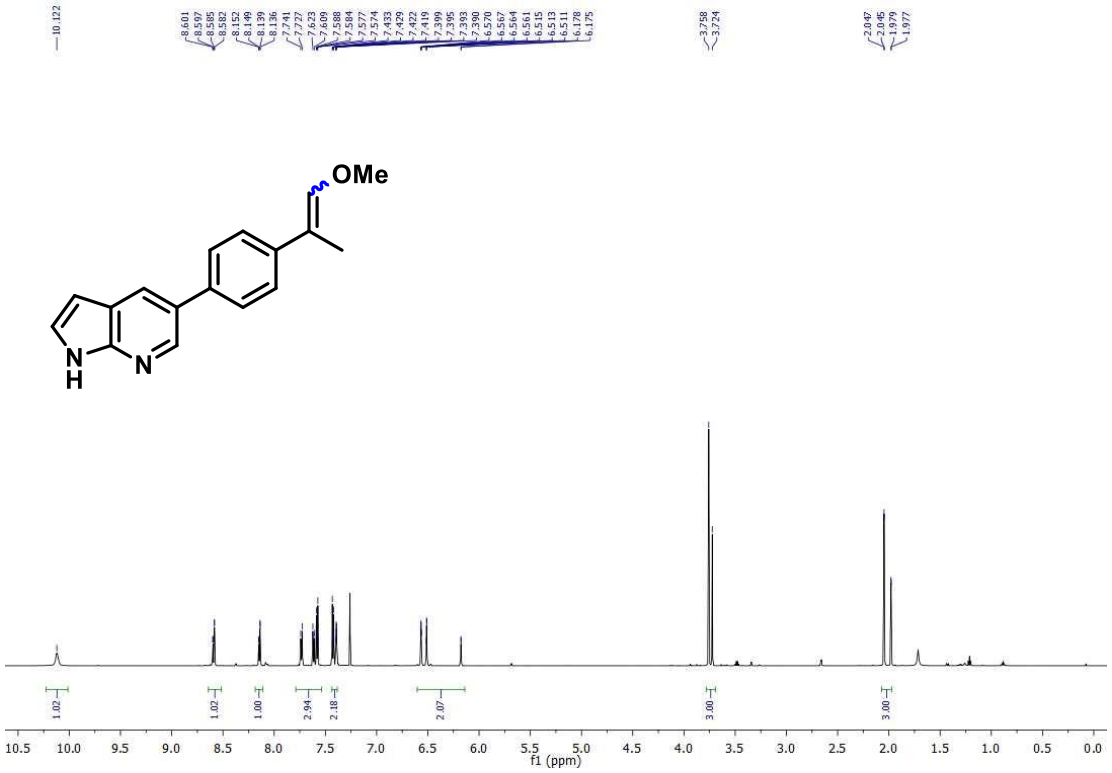
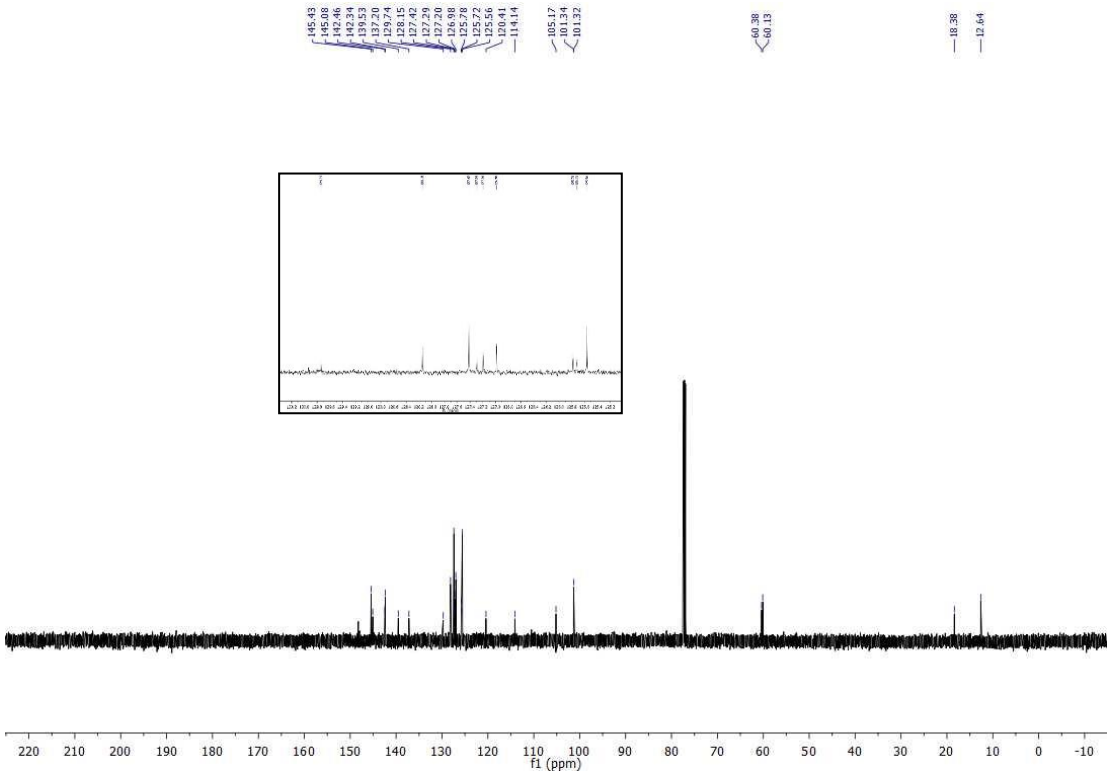
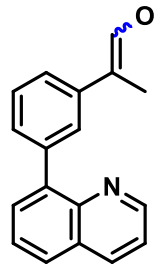
1.03
1.00
3.00
f1 (ppm)




f1 (ppm)


OMe
N
H
N
f1 (ppm)


f1 (ppm)


OMe
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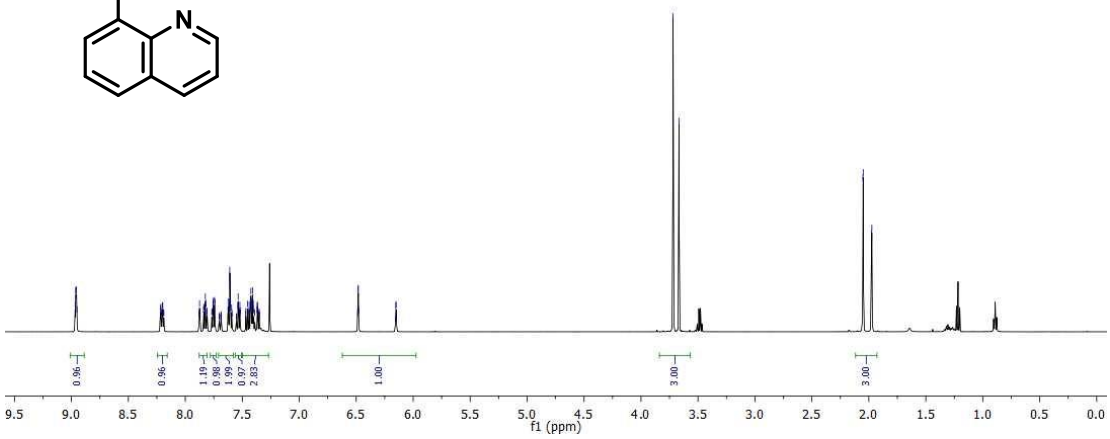
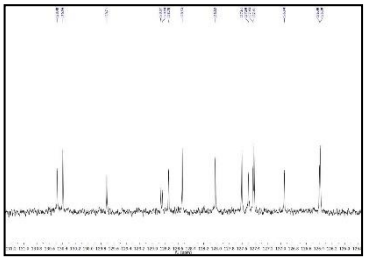
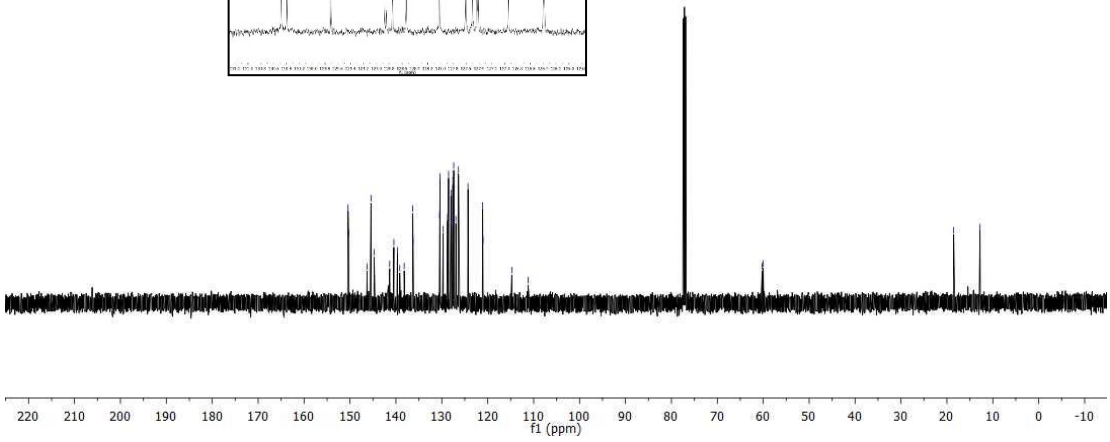
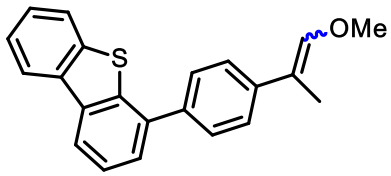
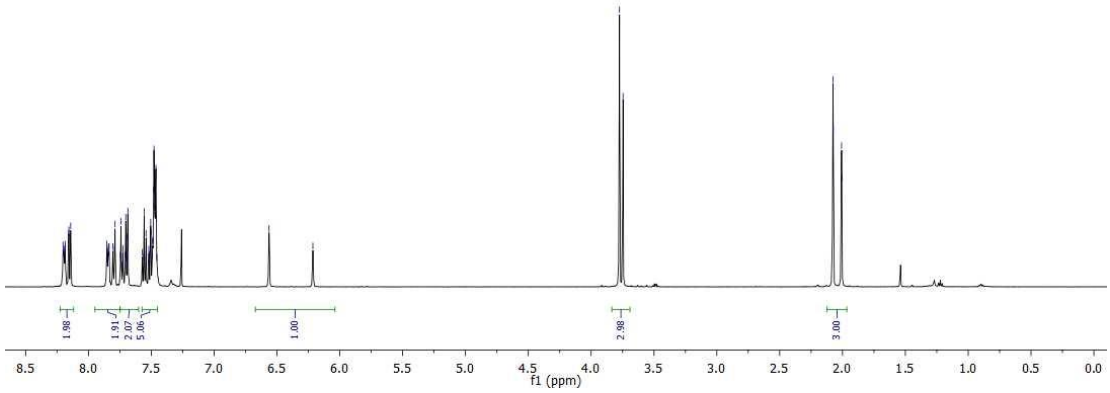
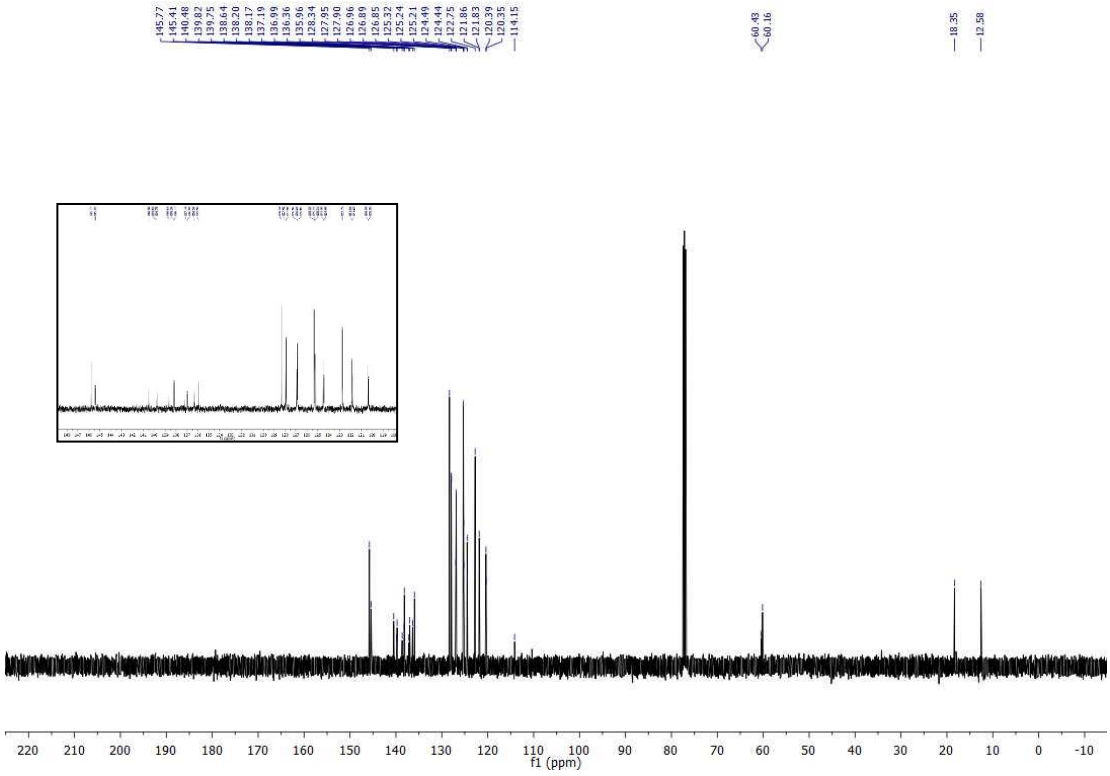

0.96
0.96
1.19
0.98
1.99
0.97
2.83
1.00
3.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

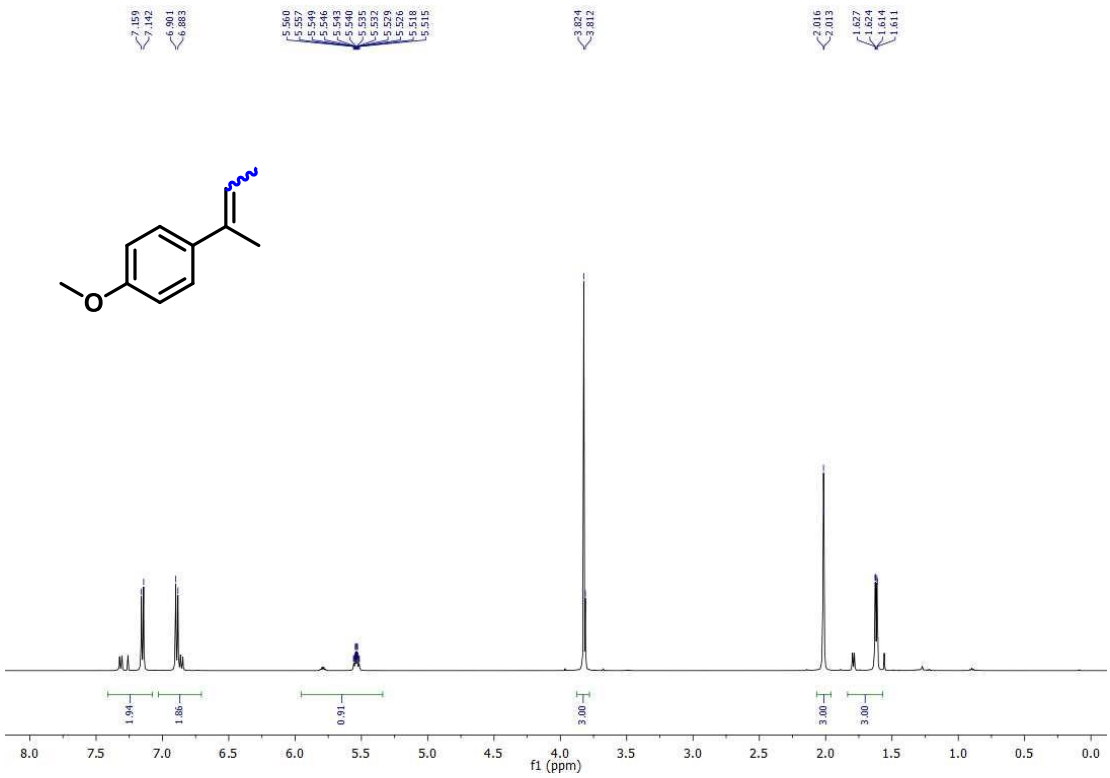


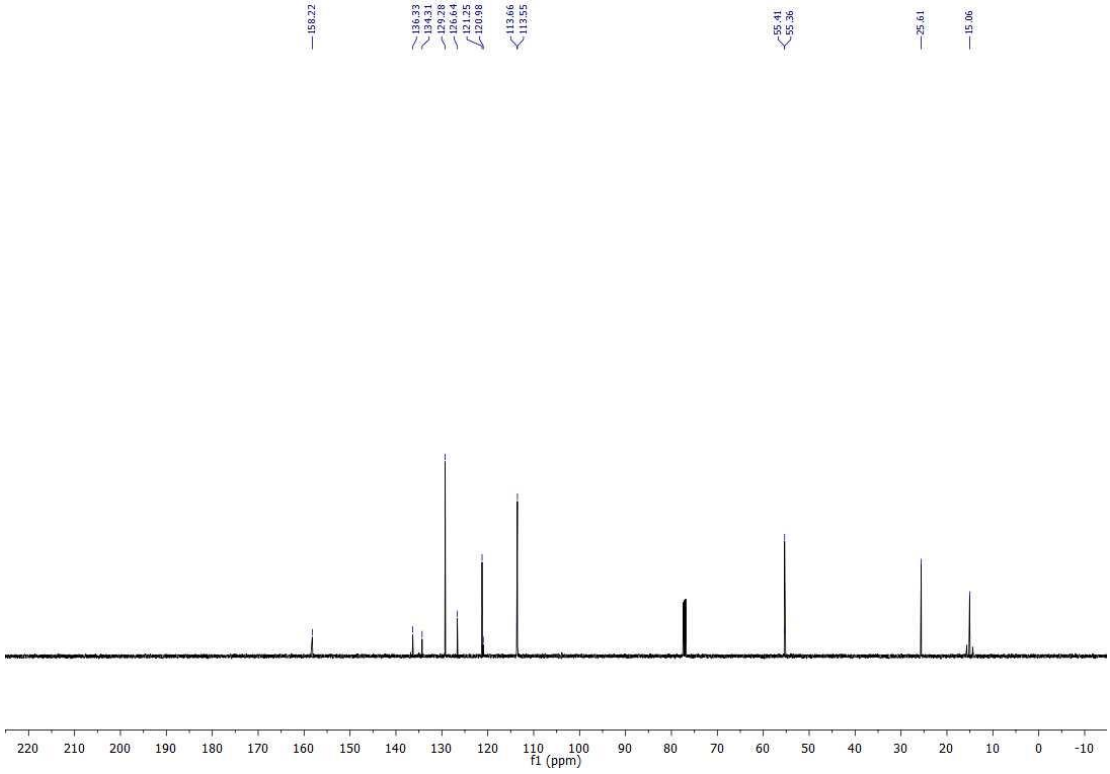

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

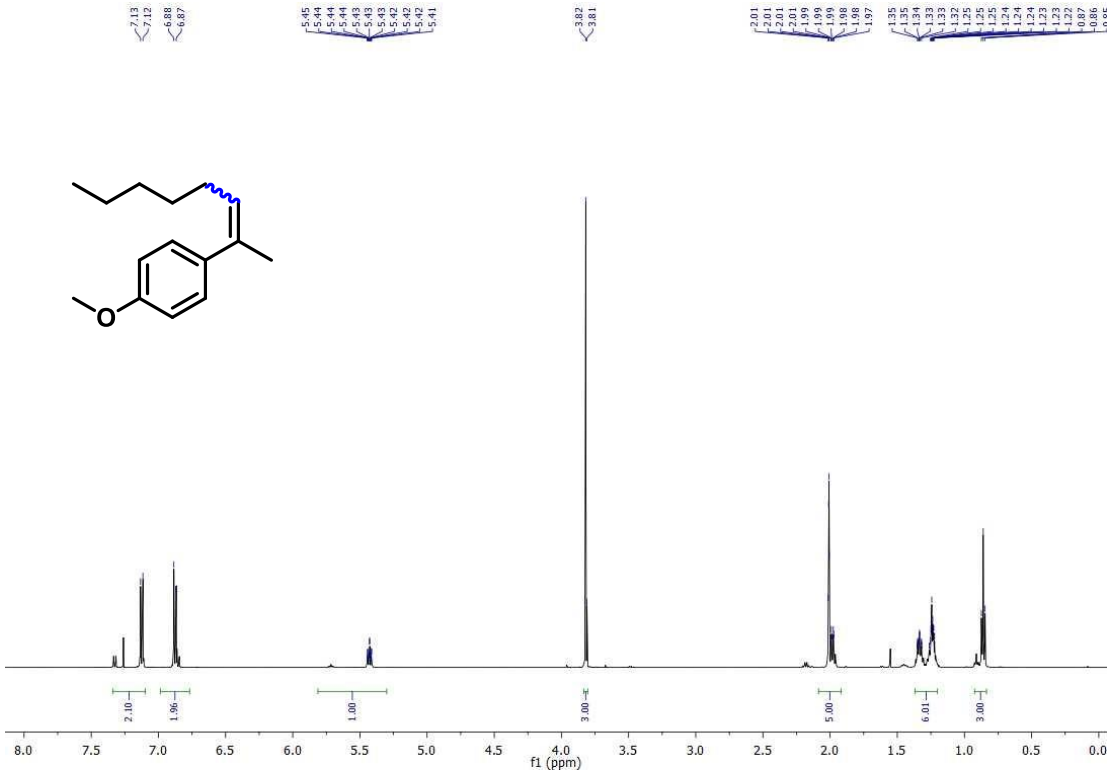

OMe
S

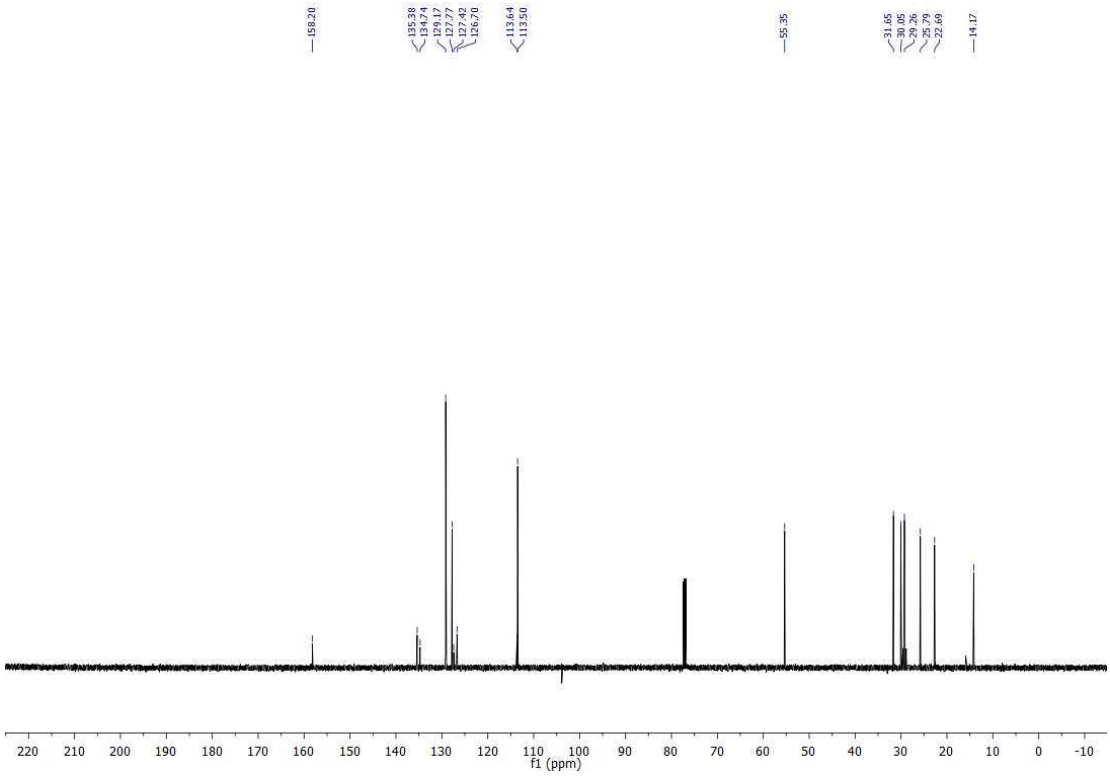

1.98
1.91
2.07
5.00
1.00
2.98
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

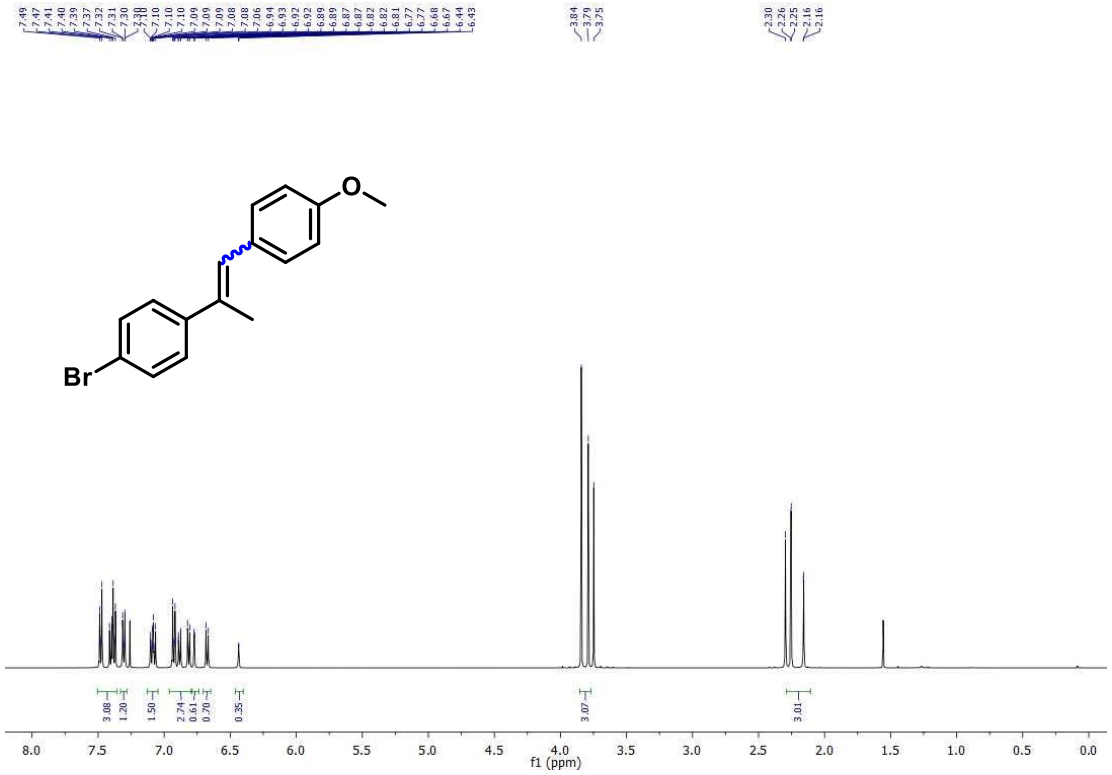

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.159
7.142
6.901
6.883
5.560
5.557
5.549
5.546
5.543
5.540
5.535
5.532
5.529
5.526
5.518
5.515
3.824
3.812
2.016
2.013
1.627
1.624
1.614
1.611
O
1.94
1.86
0.91
3.00
3.00
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


158.22
136.33
134.31
129.28
126.64
121.25
120.98
113.66
113.55
55.41
55.36
25.61
15.06
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
f1 (ppm)


f1 (ppm)


O
Br
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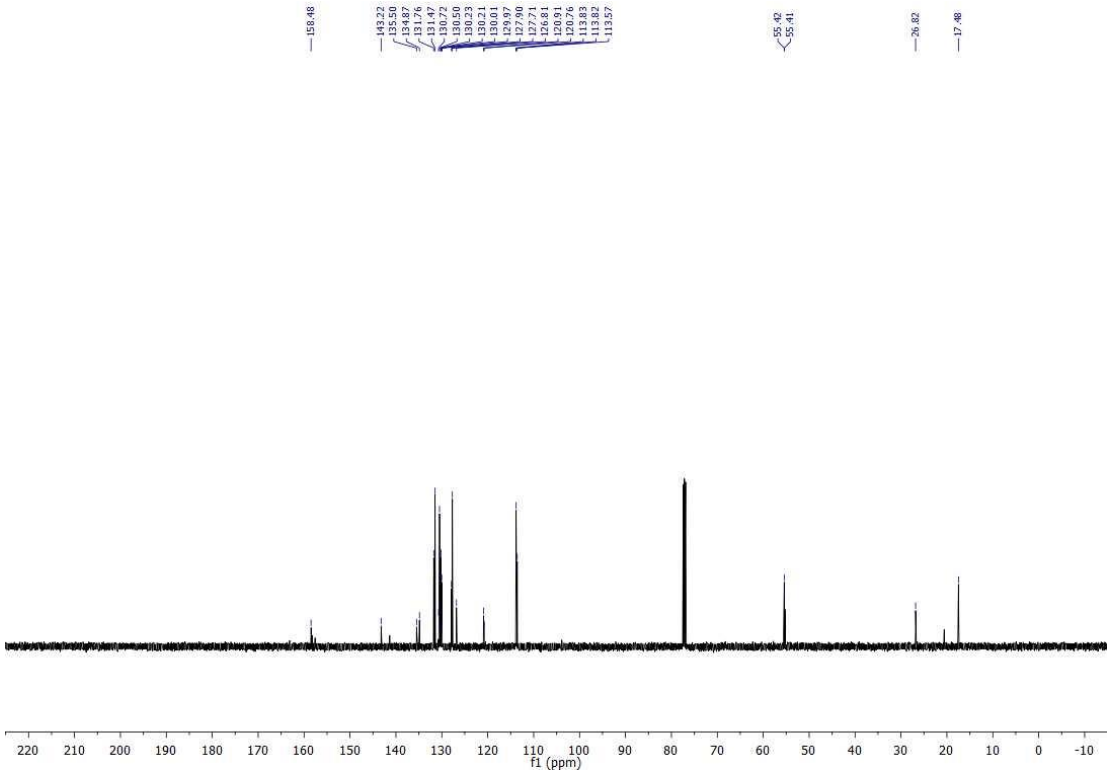
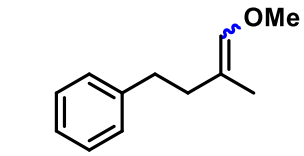
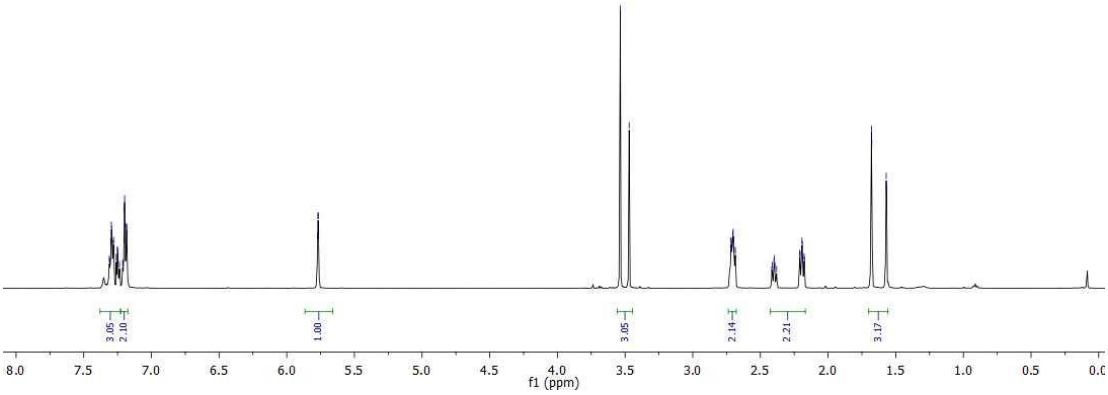
1.20
1.50
2.74
0.61
0.70
0.35
3.07
3.01
f1 (ppm)


f1 (ppm)


OMe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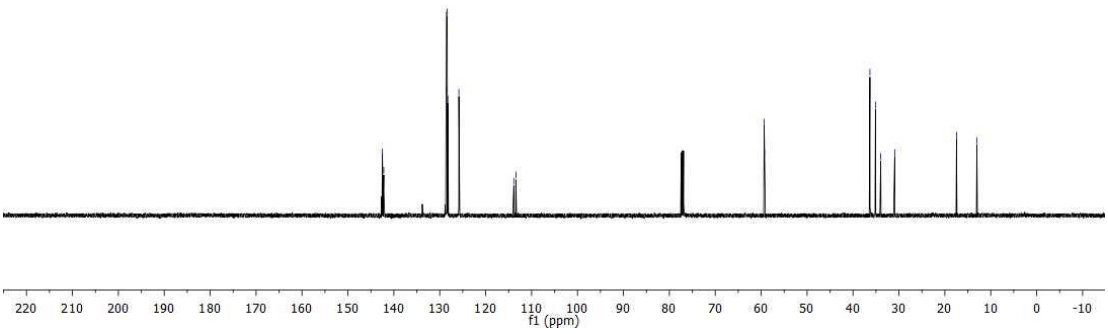
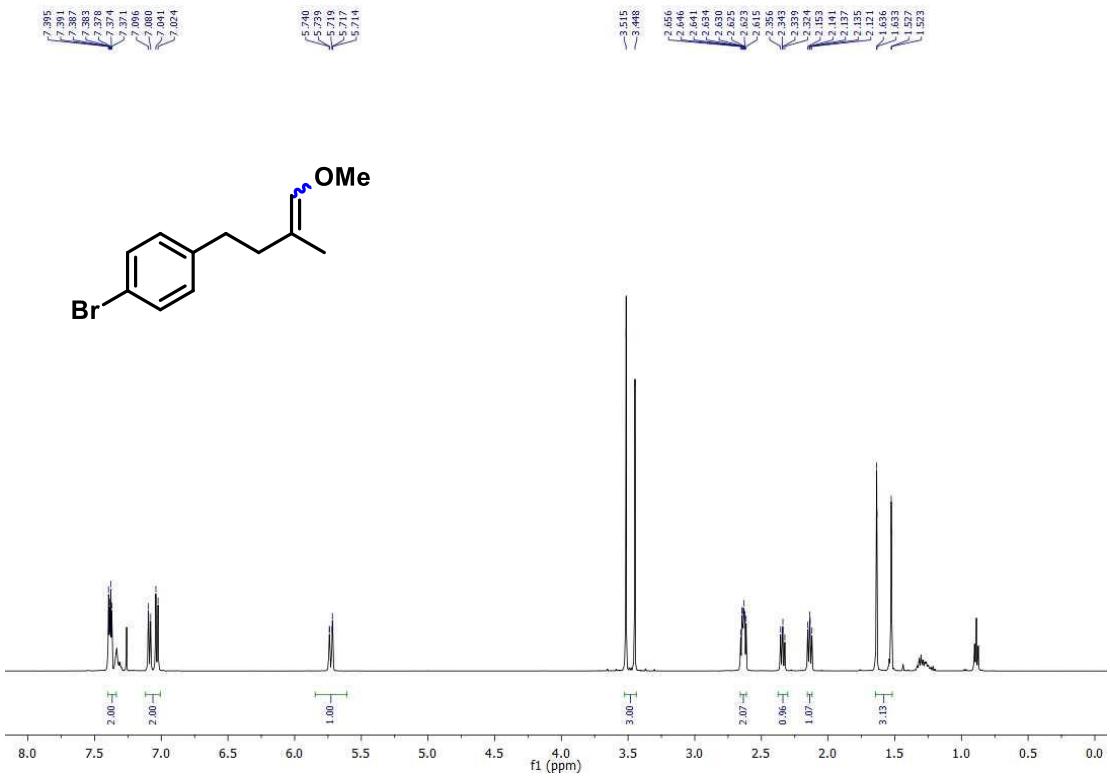
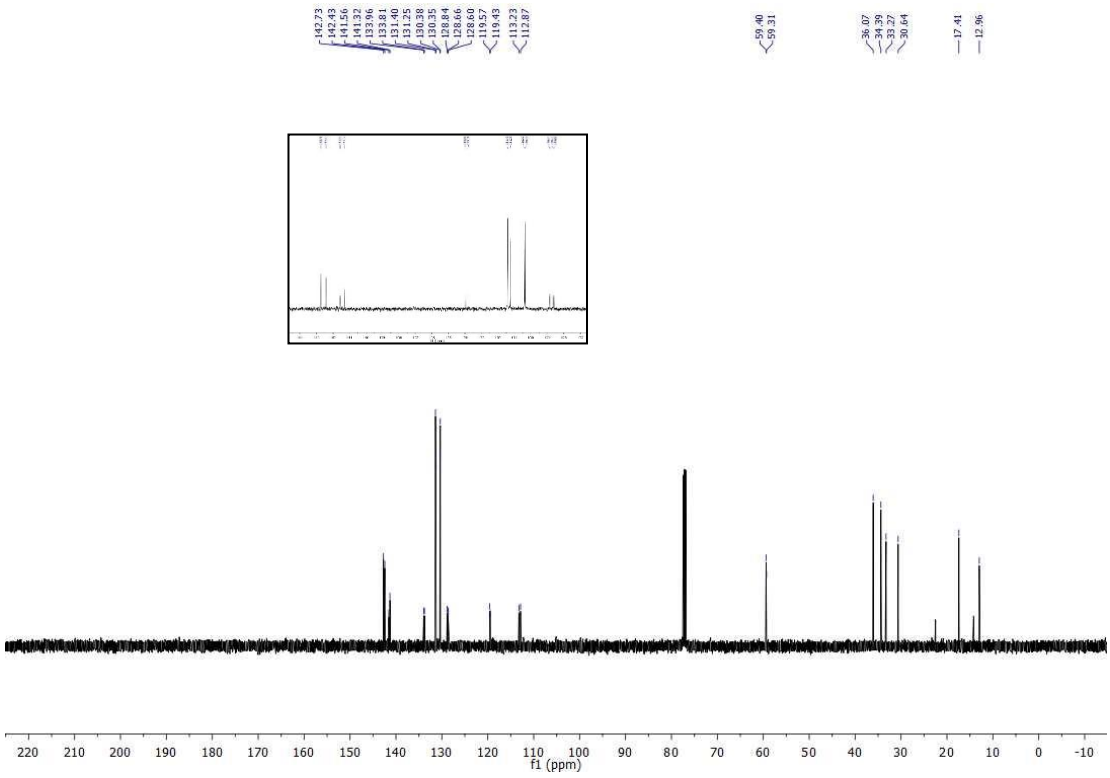
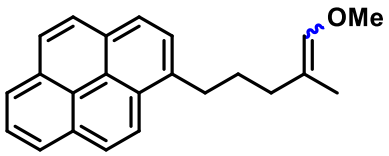
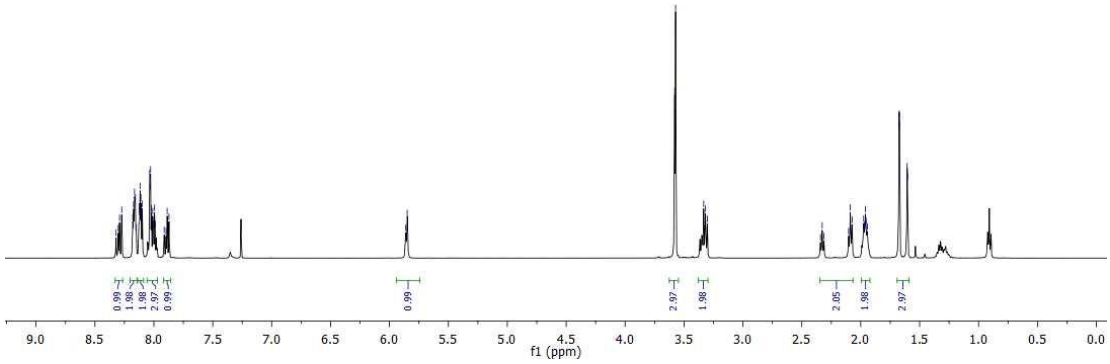
2.10
1.00
3.05
2.14
2.21
3.17
f1 (ppm)


f1 (ppm)


OMe
Br
f1 (ppm)


f1 (ppm)


OMe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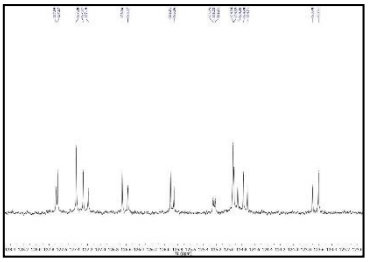
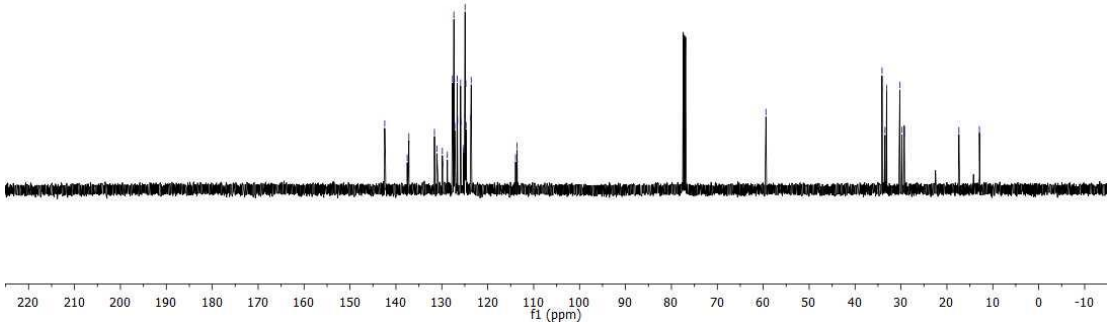
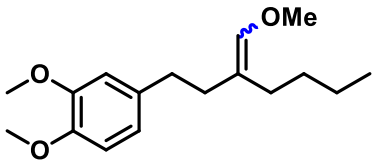
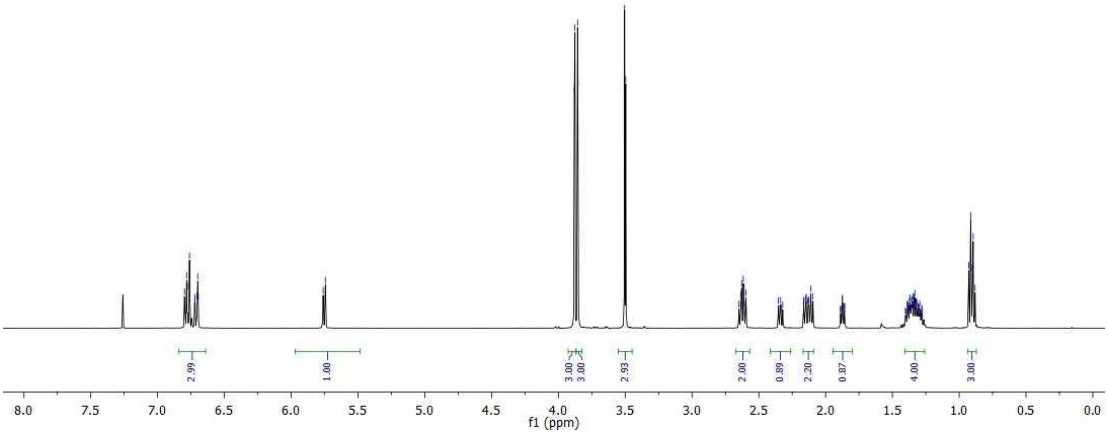
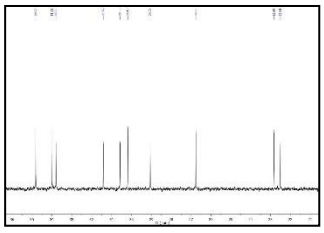
0.99
0.99
2.97
1.98
2.05
1.98
2.97
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

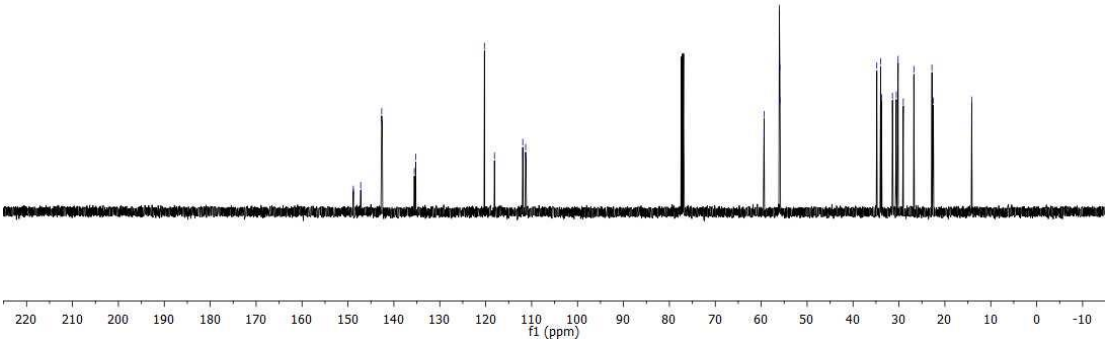



220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OMe
O
O


2.99
1.00
3.00
3.00
2.93
2.00
0.89
2.20
0.87
4.00
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)




220
210
200
190
180
170
160
150
140
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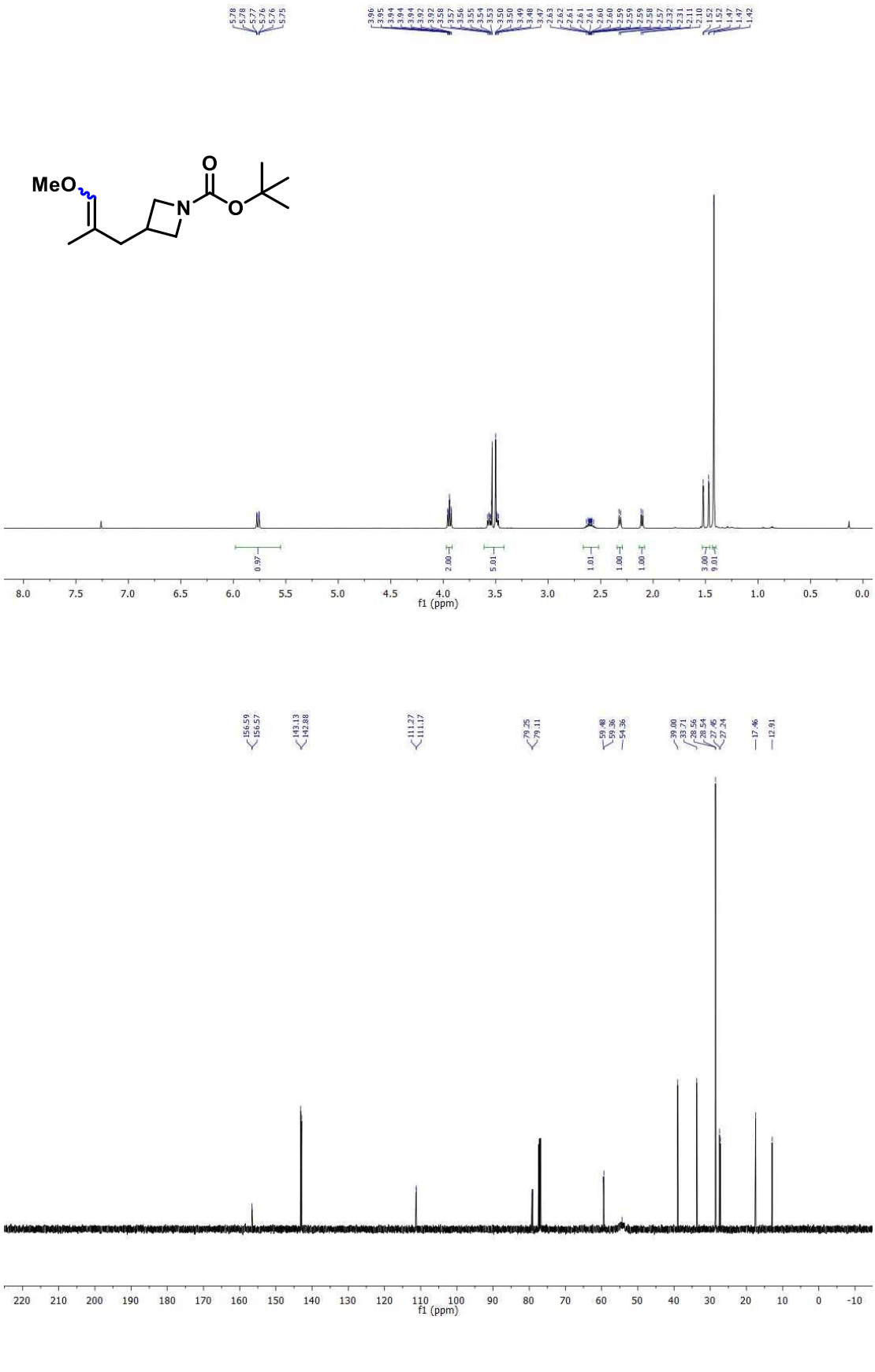
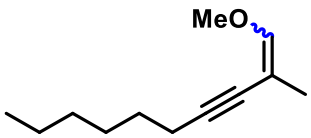
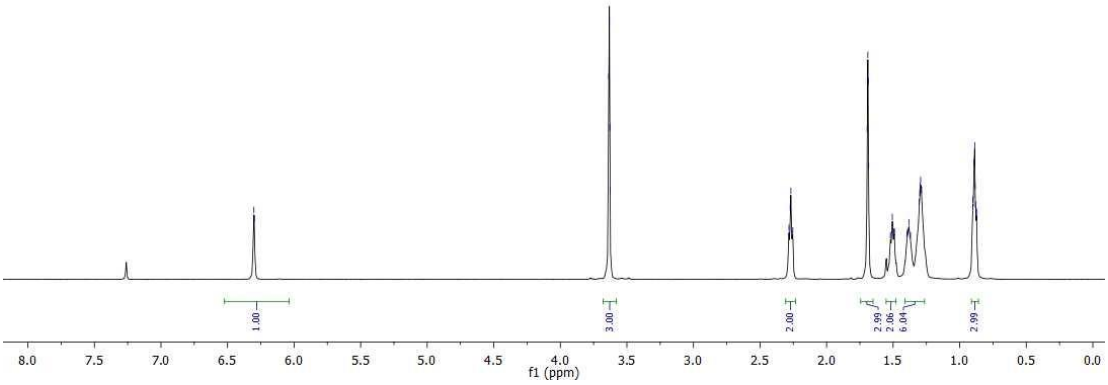
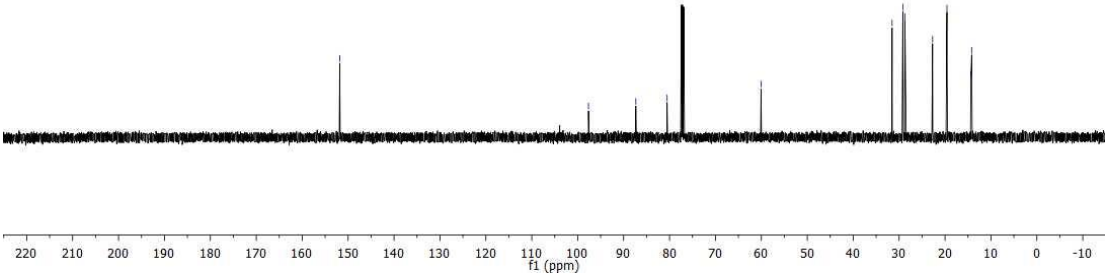
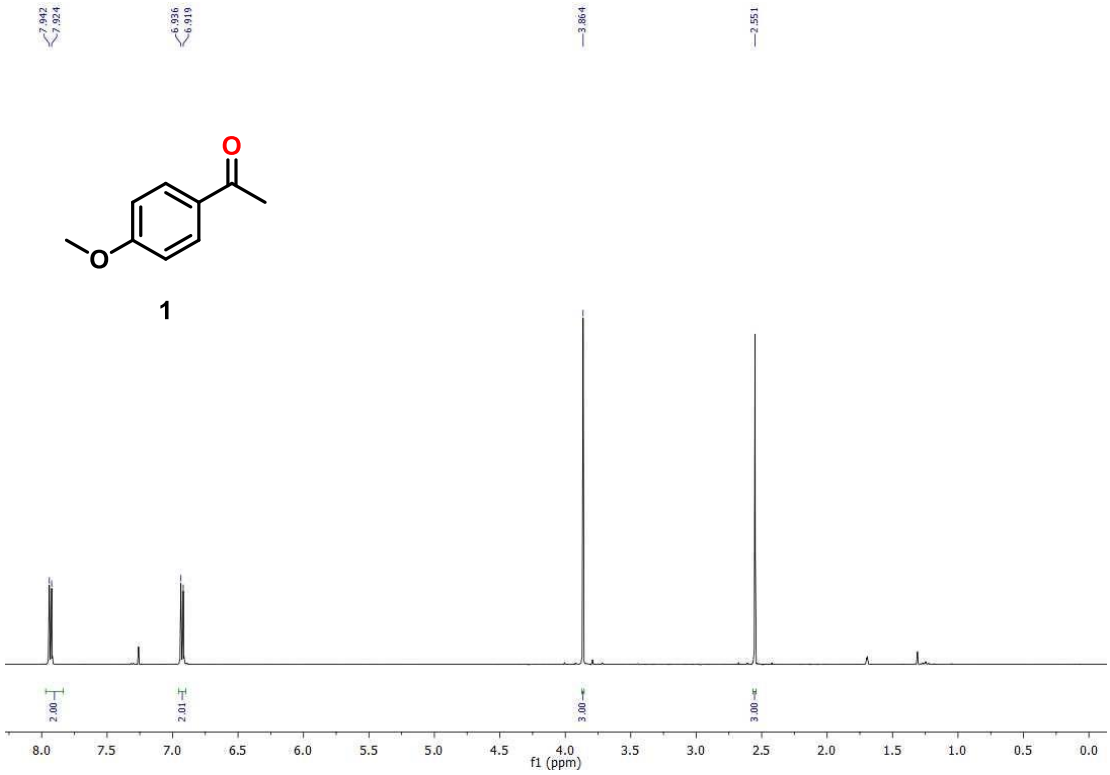
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


MeO
O
N
O
f1 (ppm)
f1 (ppm)


MeO


f1 (ppm)


f1 (ppm)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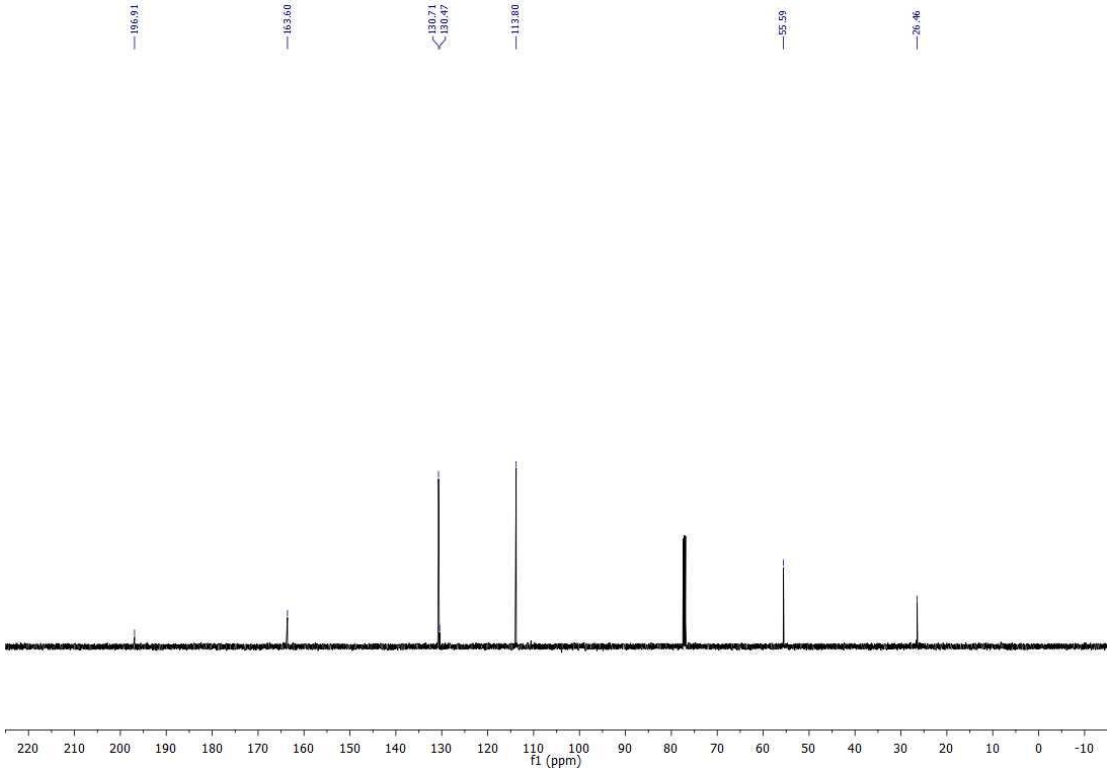
6.936
6.919
3.864
2.551
O
O
1
2.00
2.01
3.00
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


196.91
163.60
130.71
130.47
113.80
55.59
26.46
220
210
200
190
180
170
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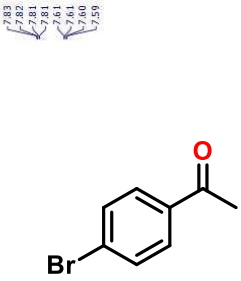
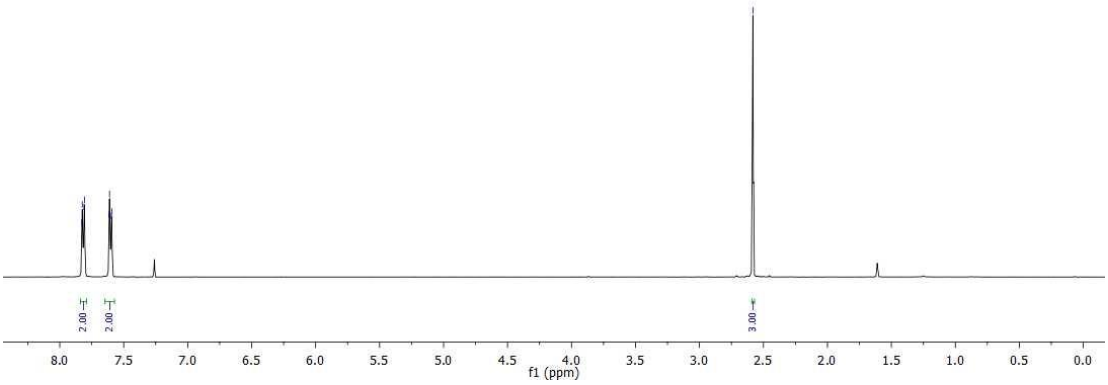
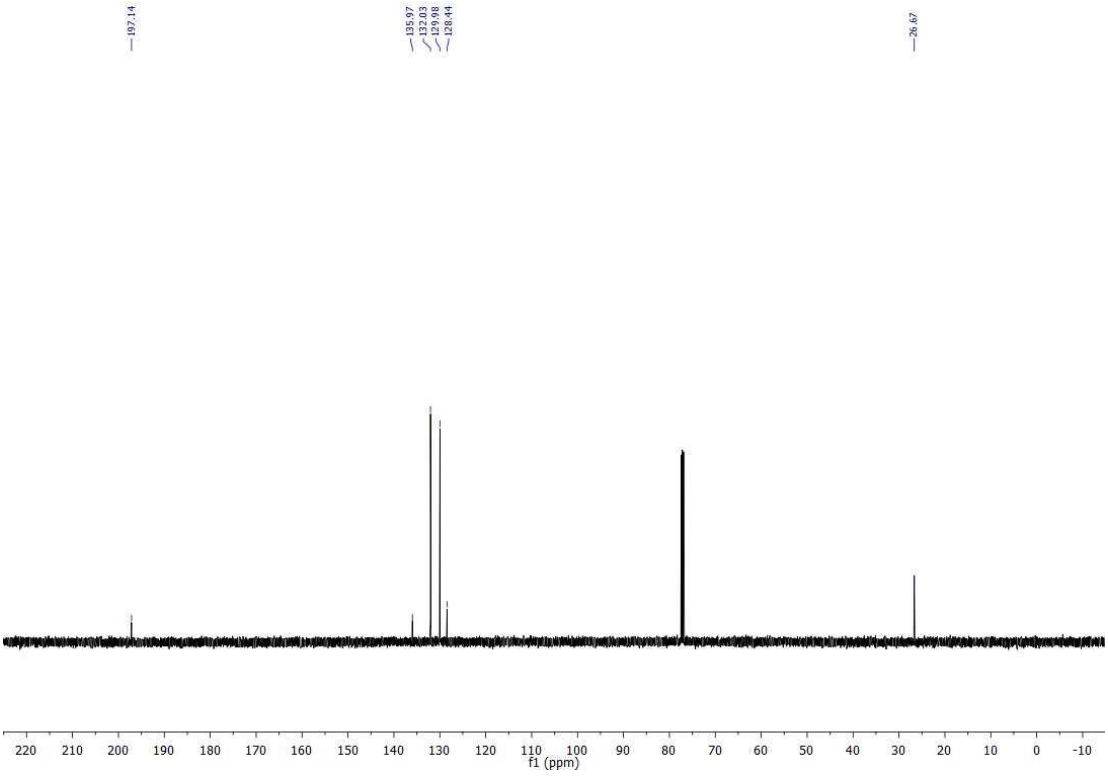
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.83
7.82
7.81
7.81
7.61
7.61
7.60
7.59
2.58
O
Br

2


2.00
2.00
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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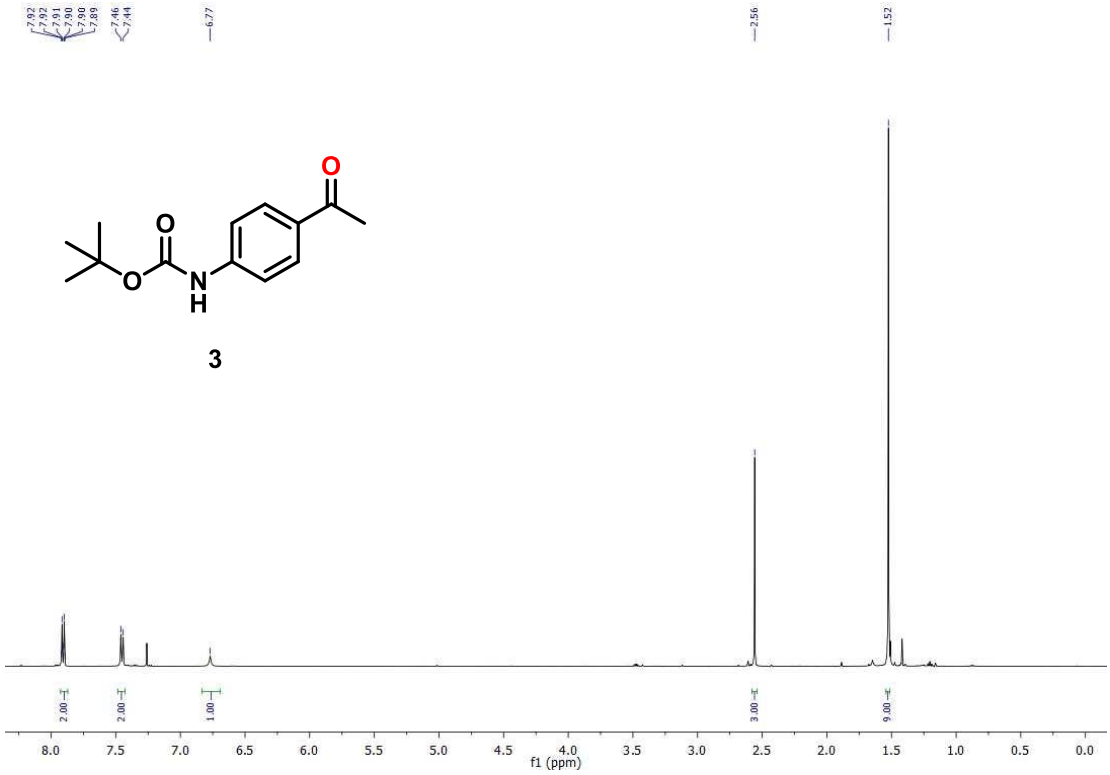
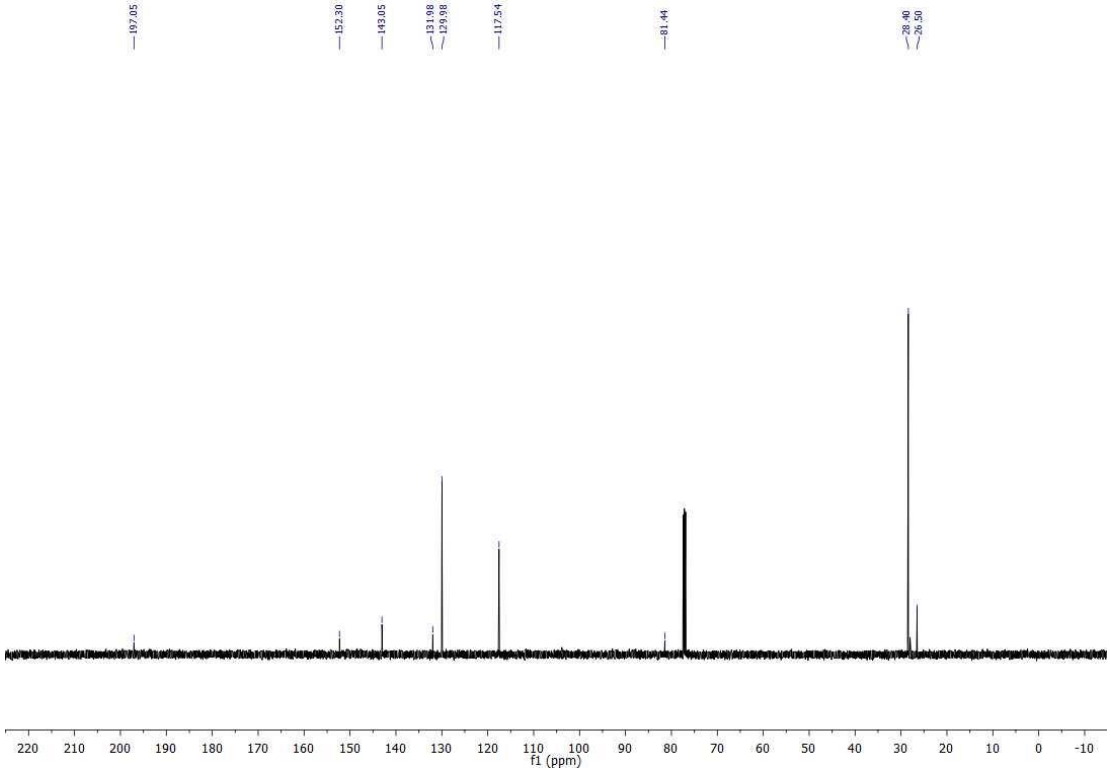
135.97
132.03
129.98
128.44
26.67
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.92
7.92
7.91
7.90
7.90
7.89
7.46
7.44
6.77
2.56
1.52
O
O
O
N
H
2.00
2.00
1.00
3.00
9.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

3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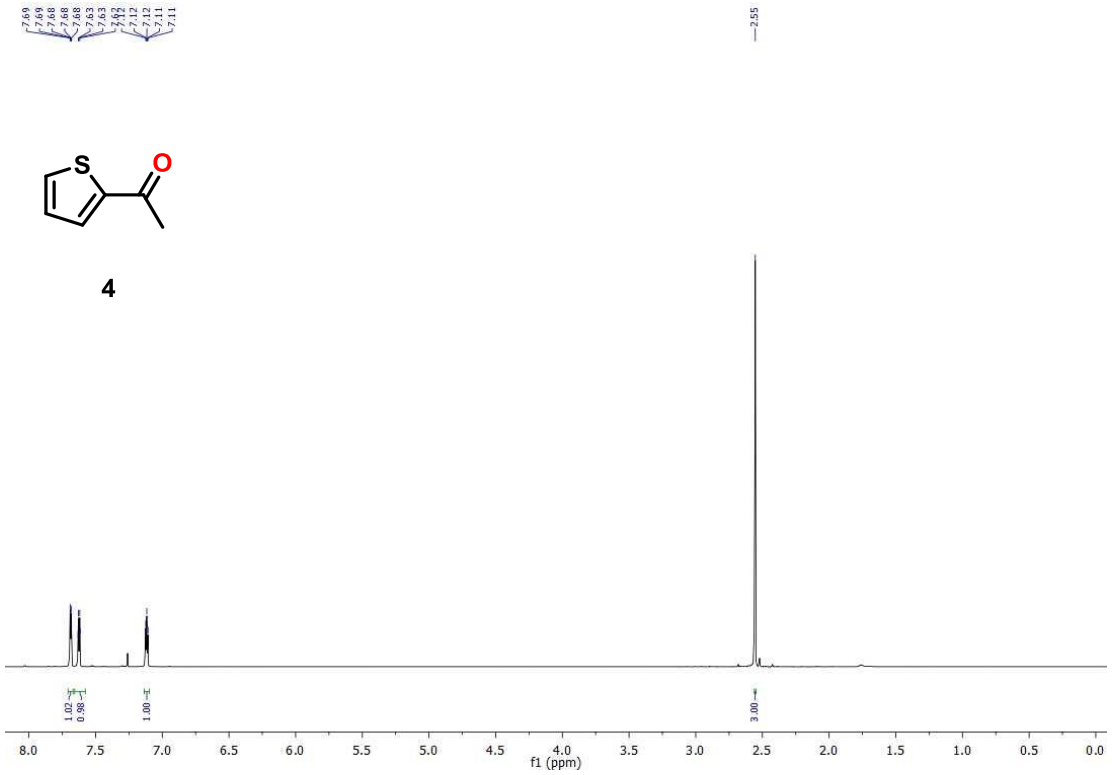
152.30
143.05
131.98
129.98
117.54
81.44
28.40
26.50
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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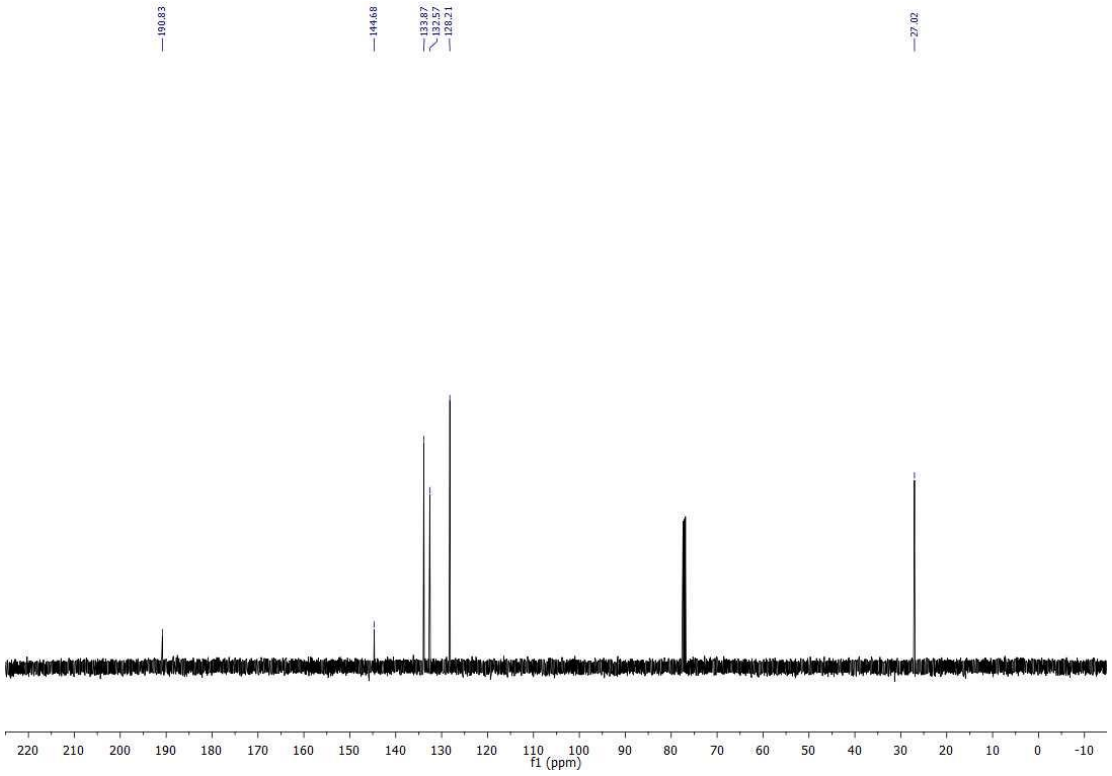
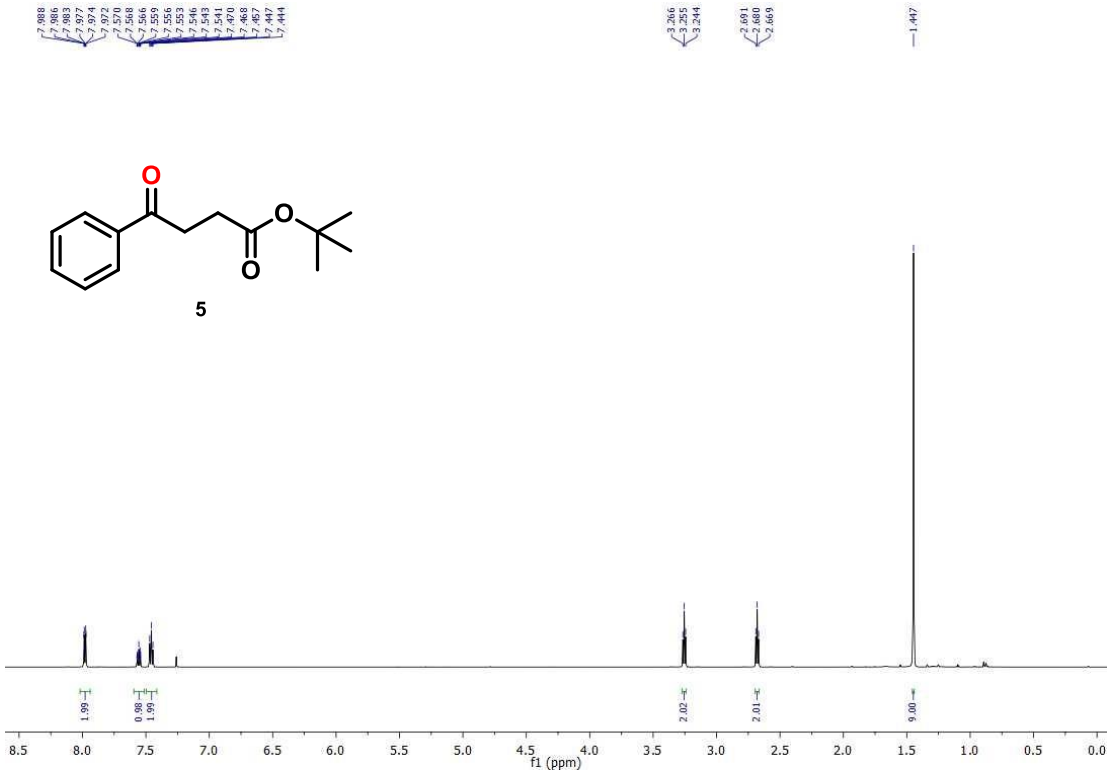
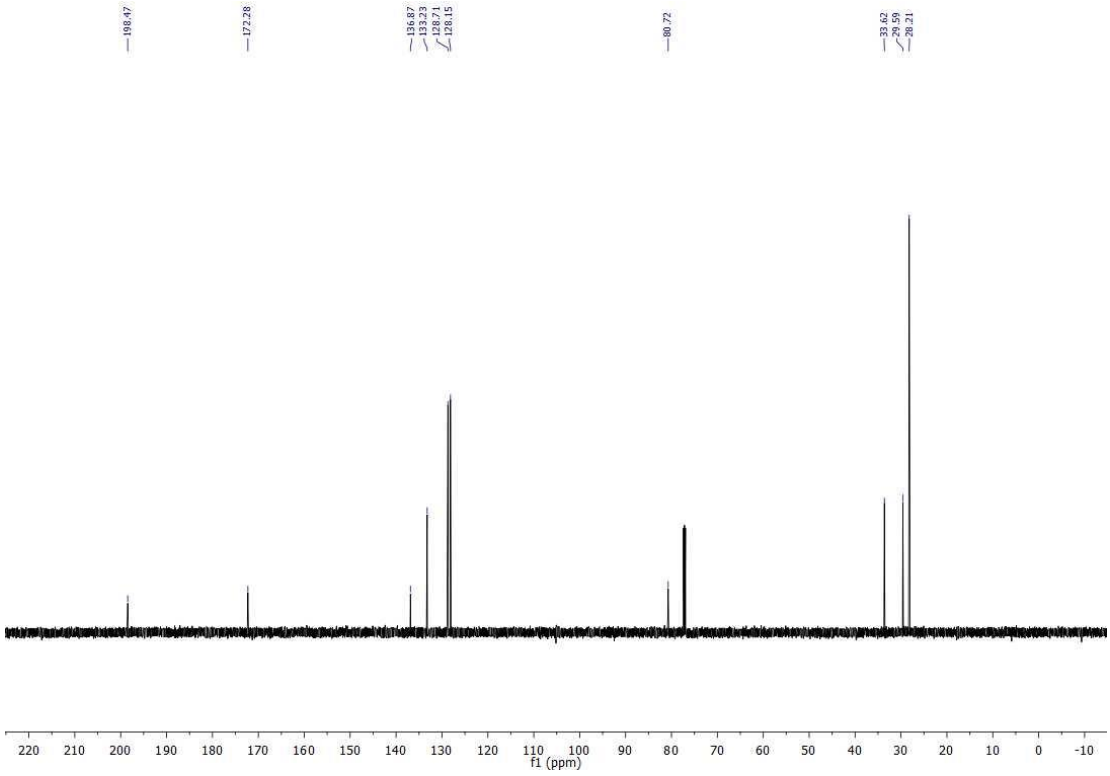
7.69
7.68
7.68
7.68
7.63
7.63
7.12
7.12
7.11
7.11
2.55
S
O
1.02
0.98
1.00
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

4


190.83
144.68
133.87
132.57
128.21
27.02
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.988
7.986
7.983
7.977
7.974
7.972
7.570
7.568
7.566
7.559
7.555
7.553
7.546
7.543
7.541
7.470
7.468
7.467
7.447
7.444
3.266
3.255
3.244
2.691
2.680
2.669
1.447
O
O
O
1.99
0.98
1.99
2.02
2.01
9.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

5


198.47
173.28
136.87
133.23
128.71
128.15
80.72
39.62
29.59
28.21
220
210
200
190
180
170
160
150
140
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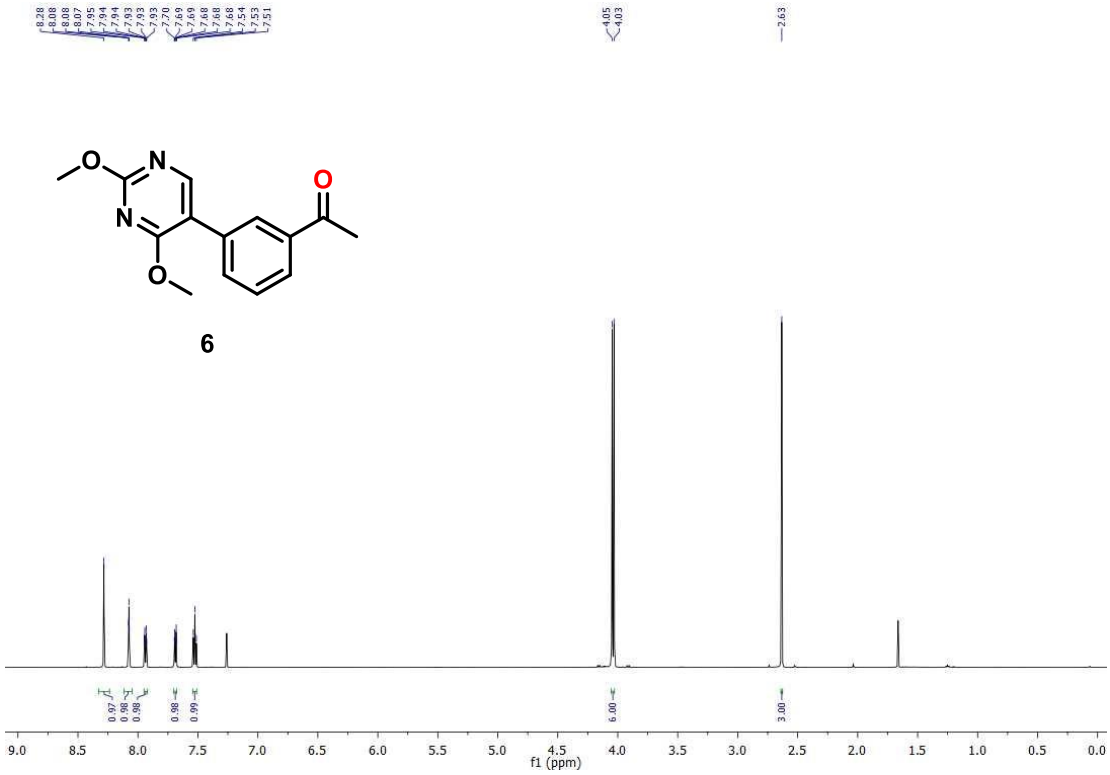
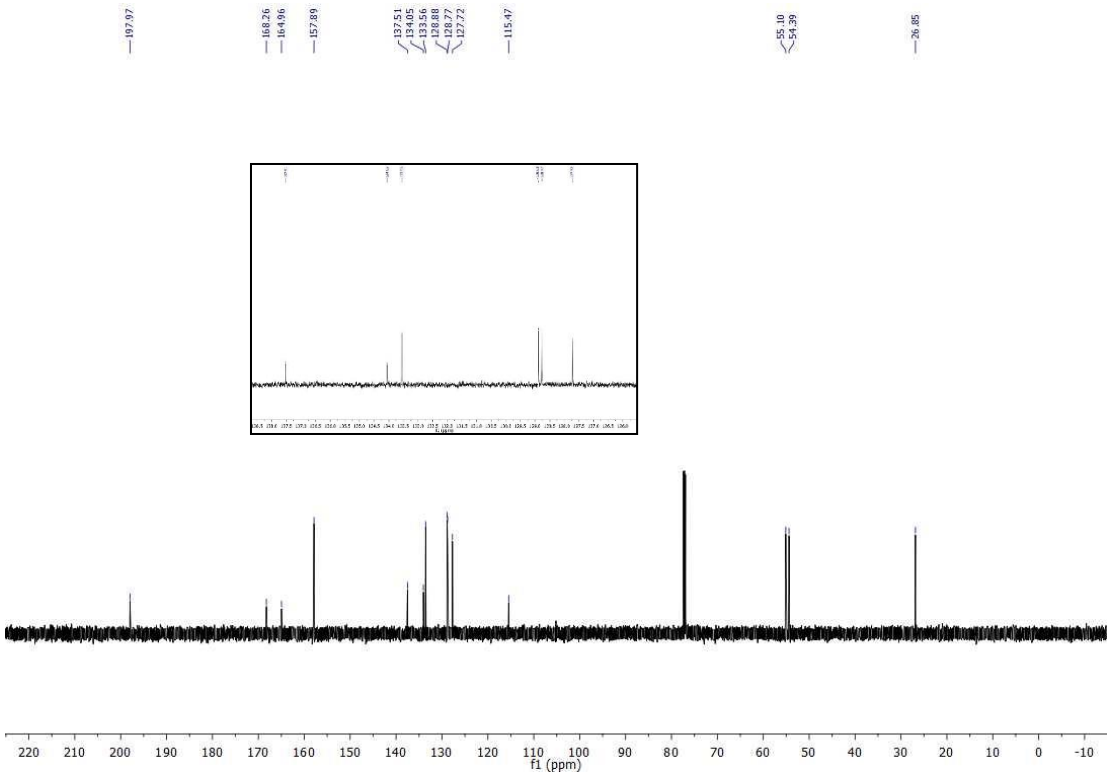
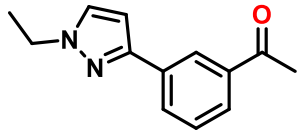
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

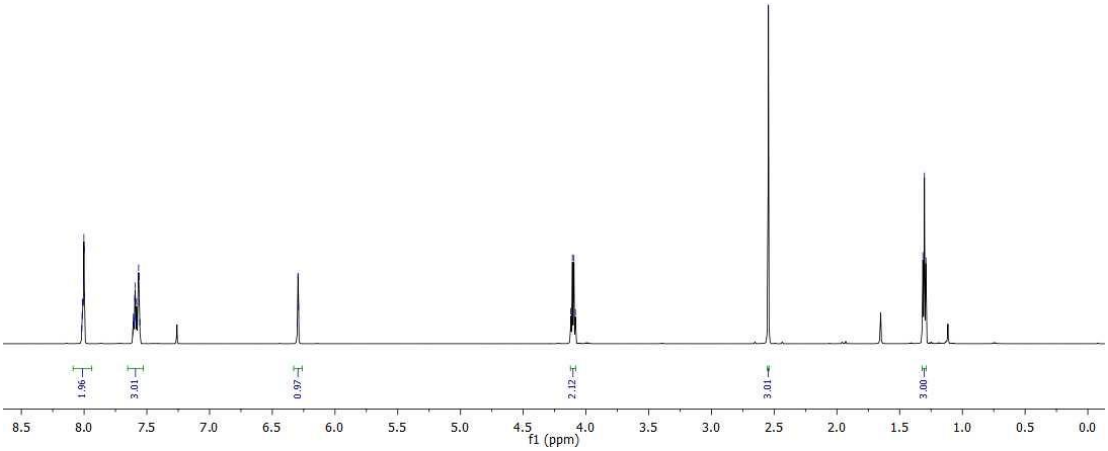

8.28
8.08
8.08
8.07
7.95
7.94
7.94
7.93
7.93
7.93
7.70
7.69
7.69
7.68
7.68
7.68
7.54
7.53
7.51
4.05
4.03
2.63
O
N
O
N
O
0.97
0.98
0.98
0.98
0.99
6.00
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

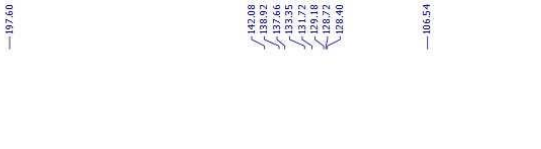
6

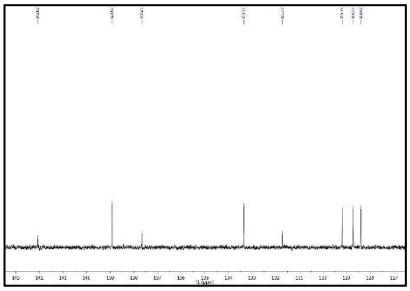

197.97
168.26
164.96
157.89
137.51
134.05
133.56
128.88
128.77
127.72
115.47
55.10
54.39
26.85
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

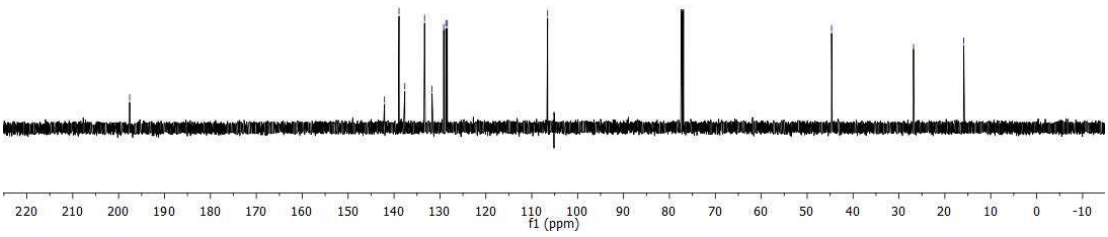


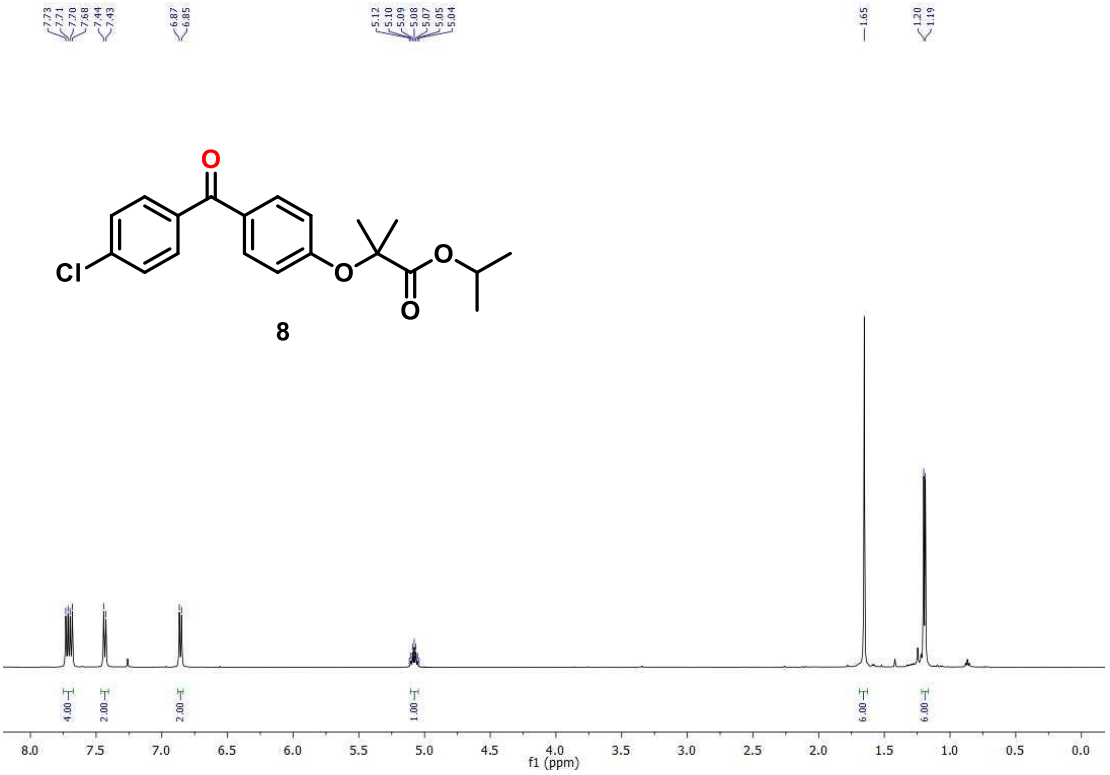
7

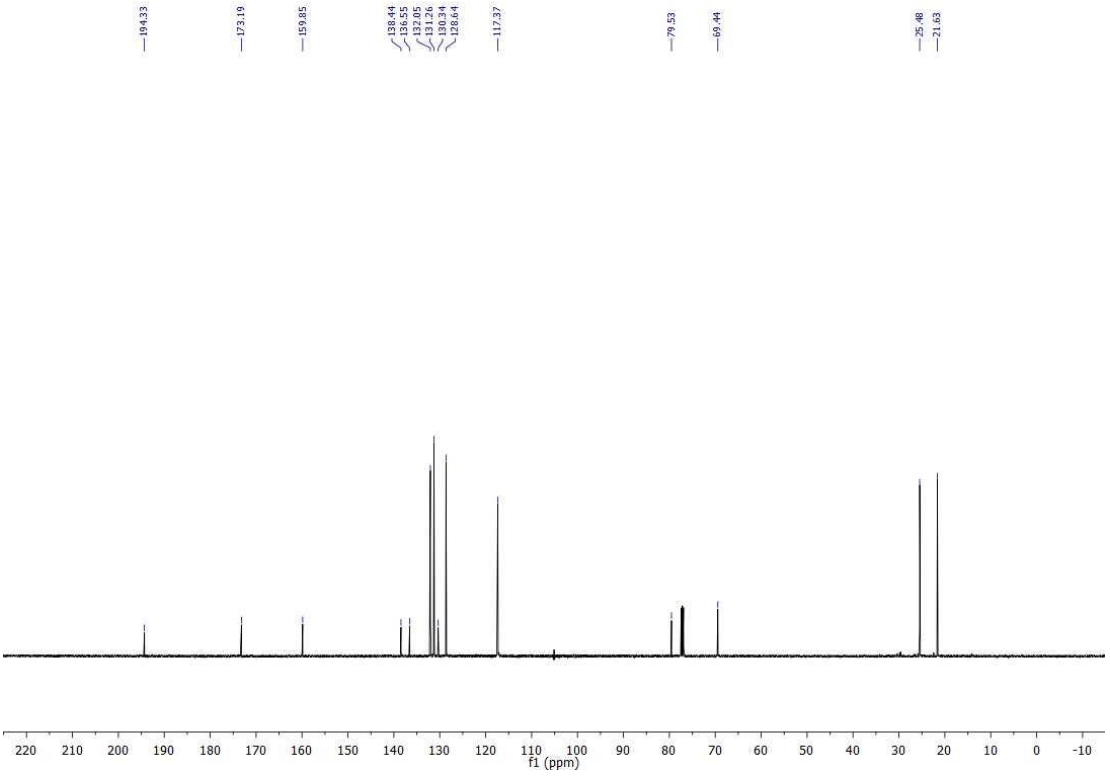


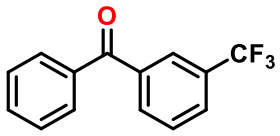




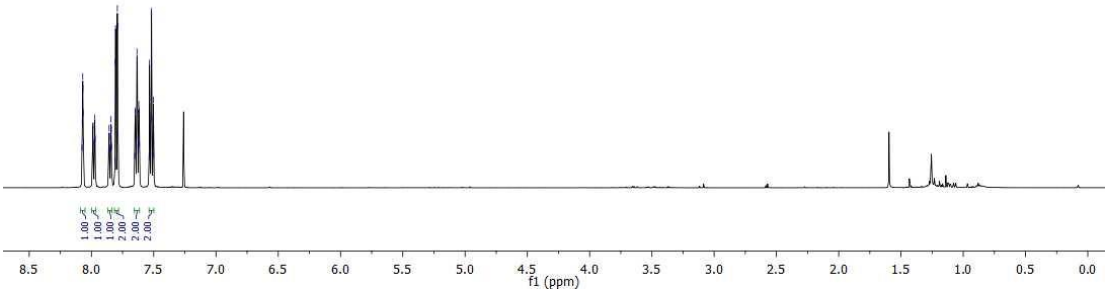


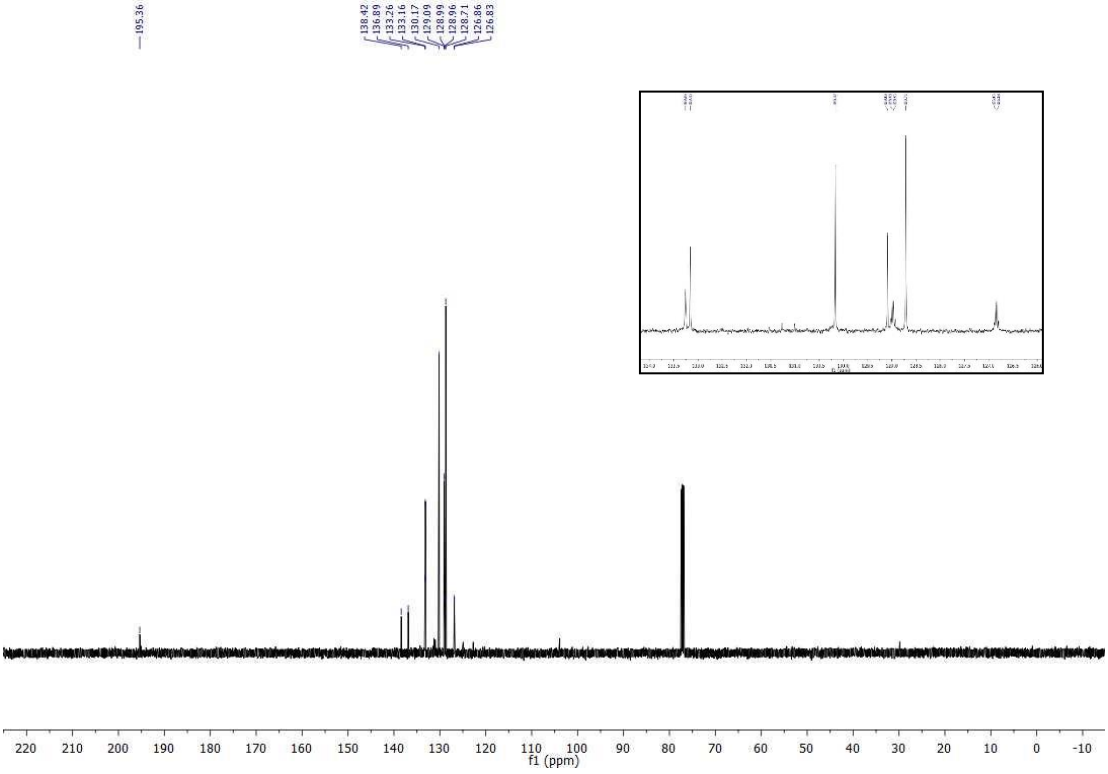

7.73
7.71
7.70
7.68
7.44
7.43
6.87
6.85
5.12
5.10
5.09
5.08
5.07
5.05
5.04
1.65
1.20
1.19
O
Cl
O
O
O
8
4.00
2.00
2.00
1.00
6.00
6.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

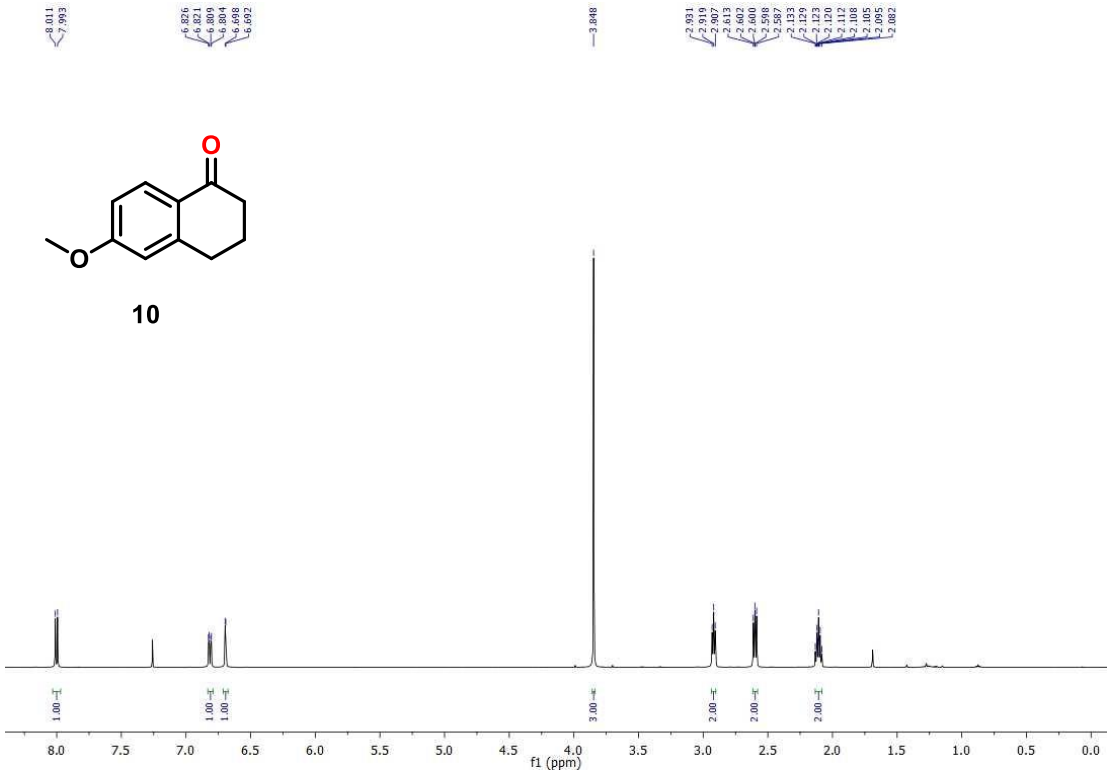

194.33
173.19
159.85
138.44
136.55
132.05
131.26
130.34
128.64
117.37
79.53
69.44
25.48
21.63
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



9



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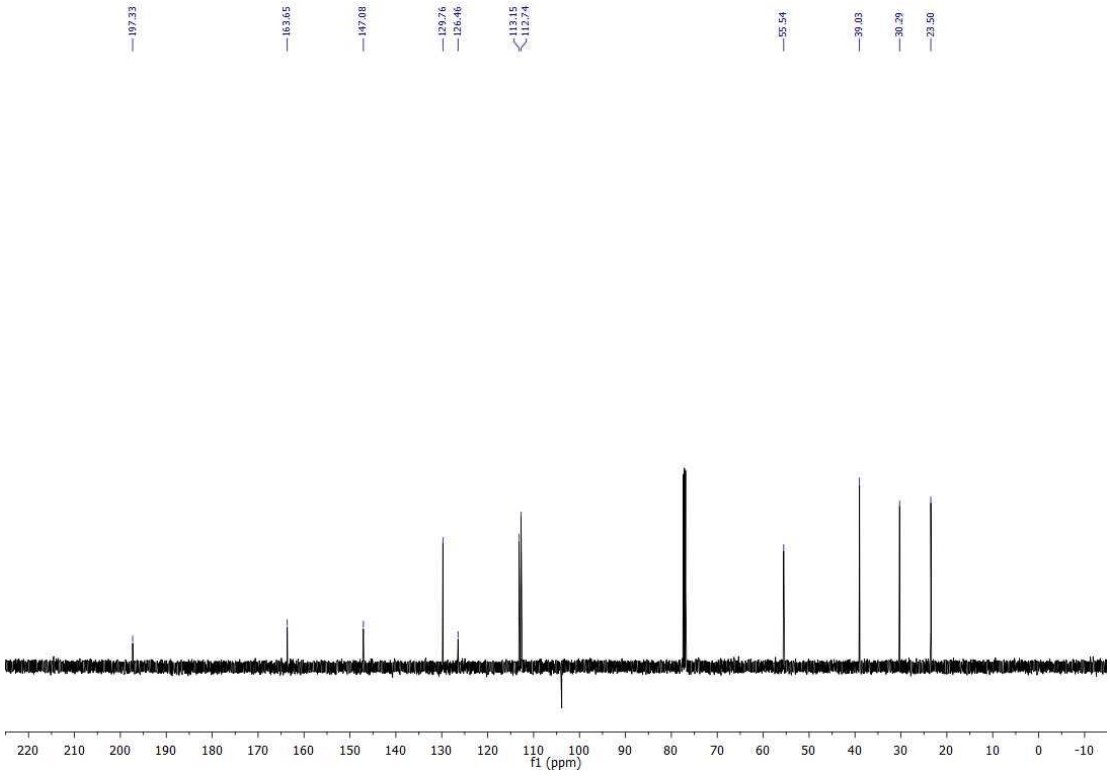
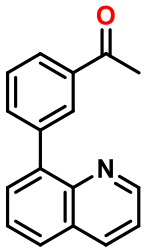
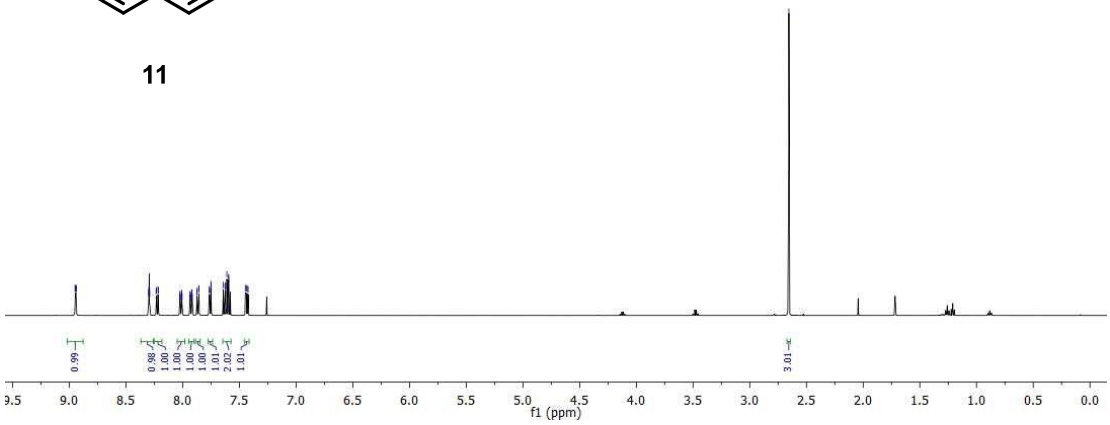
6.826
6.821
6.806
6.804
6.698
6.692
3.848
2.931
2.919
2.907
2.613
2.602
2.600
2.598
2.587
2.133
2.129
2.123
2.120
2.112
2.108
2.105
2.095
2.082
O
O
1.00
1.00
1.00
3.00
2.00
2.00
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

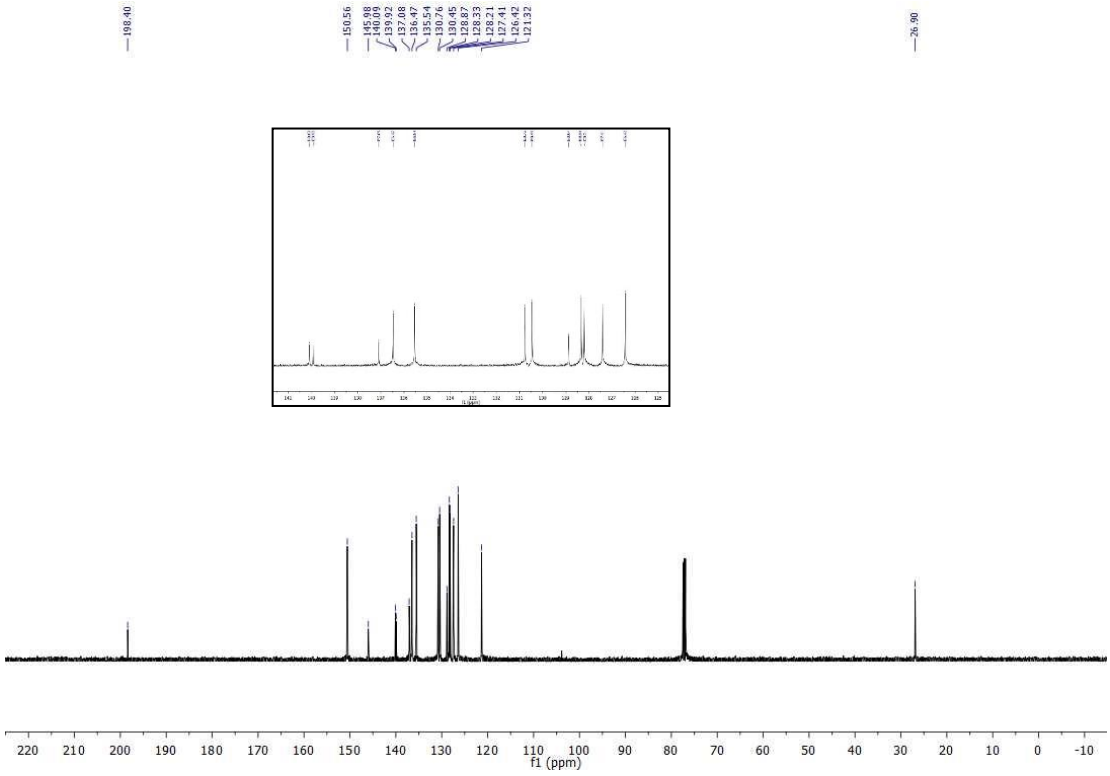
10

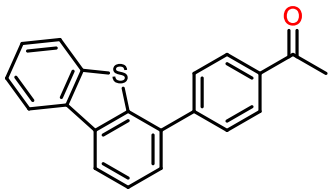

197.33
163.65
147.08
129.76
126.46
113.15
112.74
55.54
39.03
30.29
29.50
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



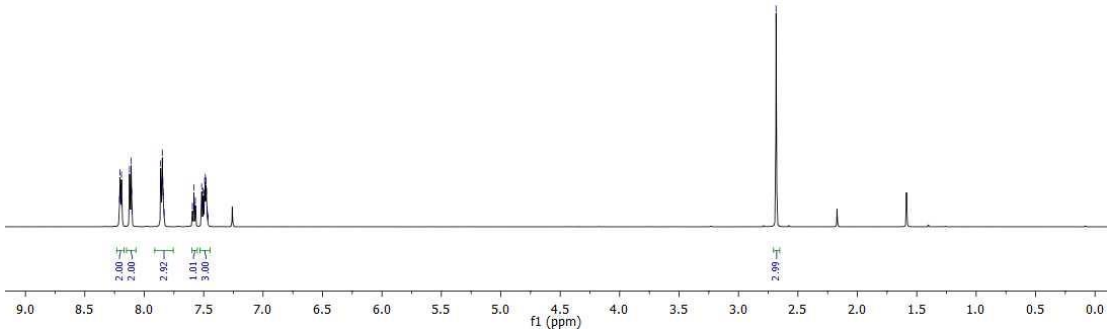
11

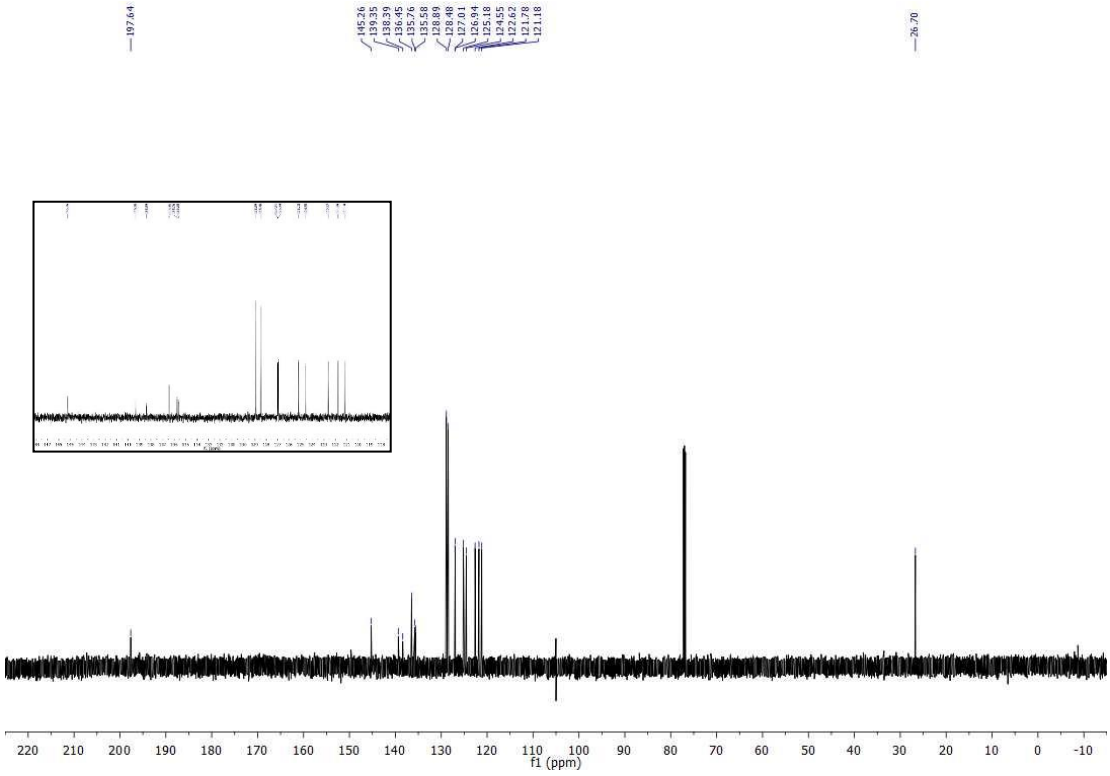


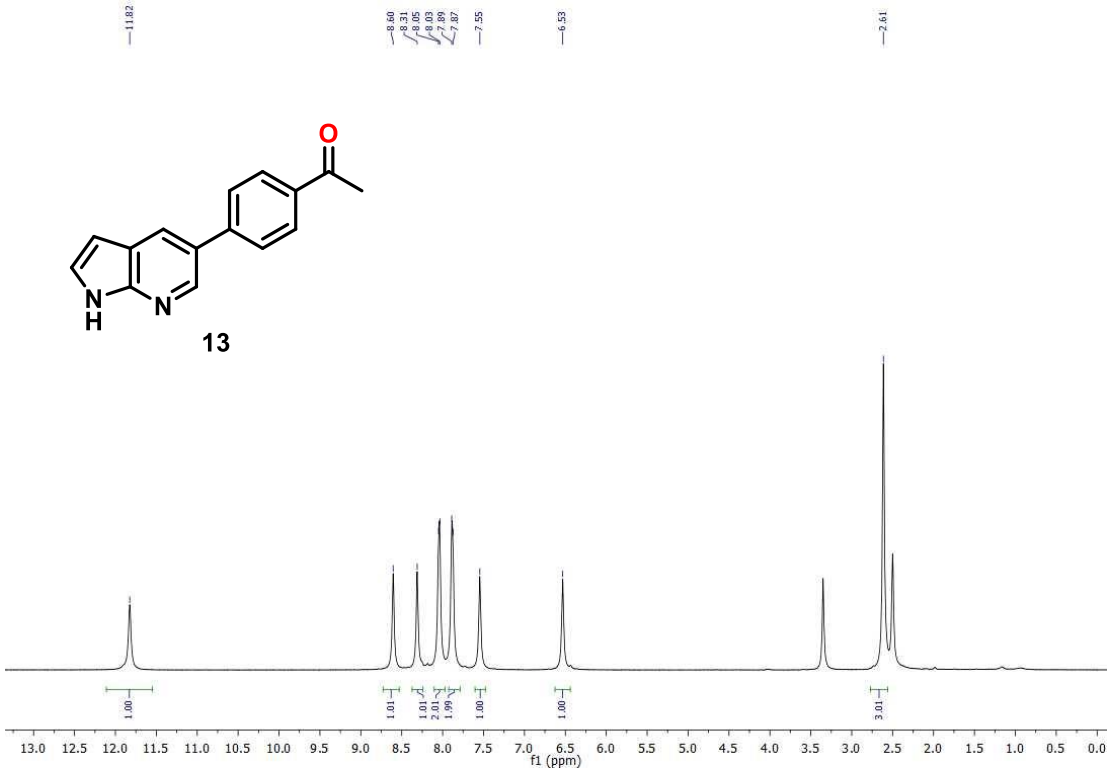




12



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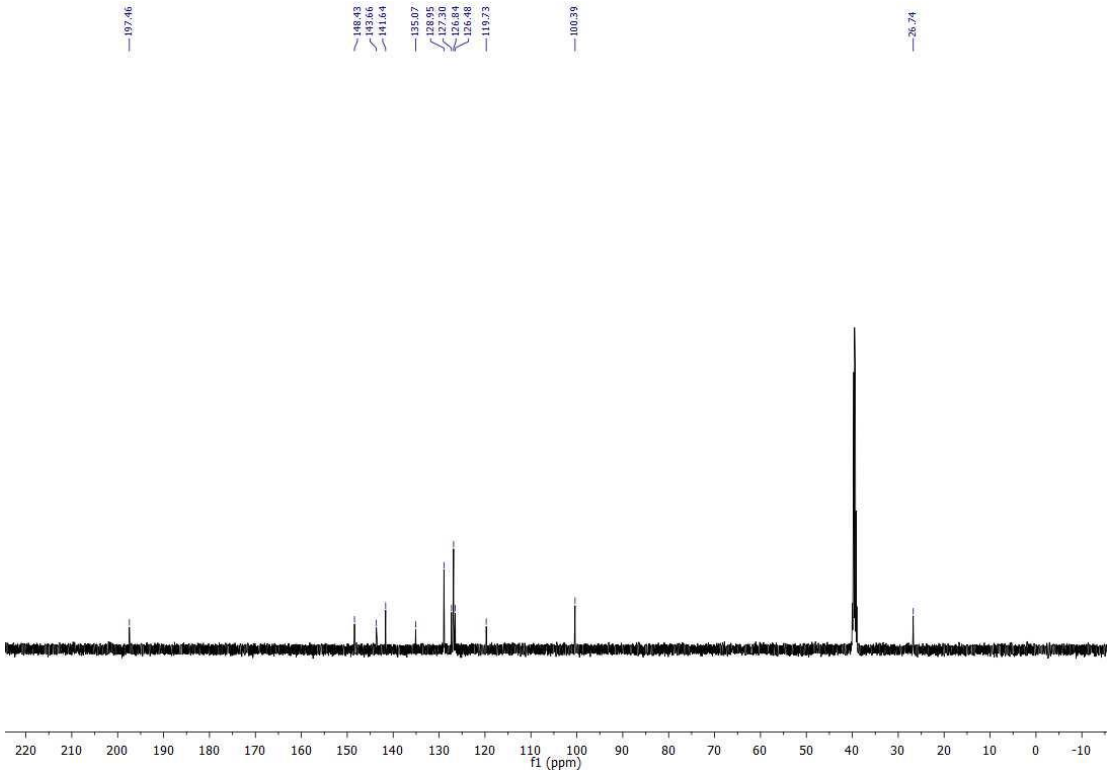
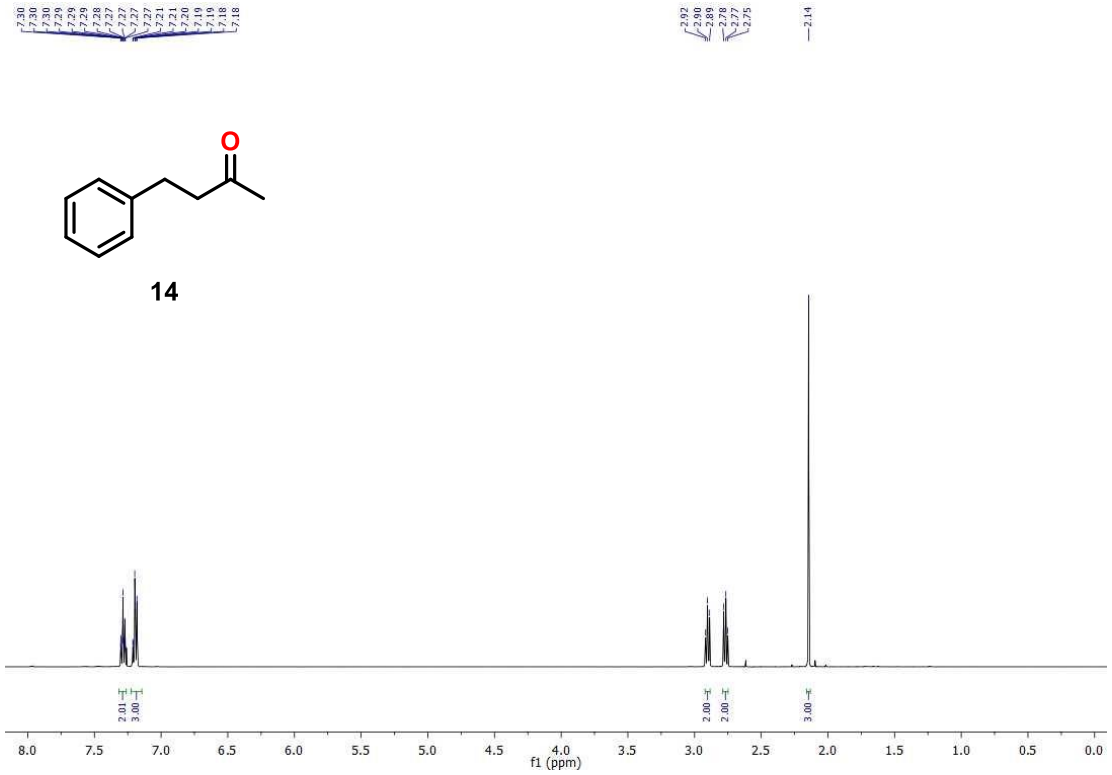
8.03
7.89
7.87
7.55
6.53
2.61
O
N
H
N
1.00
1.01
1.01
2.01
1.99
1.00
1.00
3.01
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


197.46
148.43
143.66
141.64
135.07
128.95
127.30
126.84
126.48
119.73
100.39
26.74
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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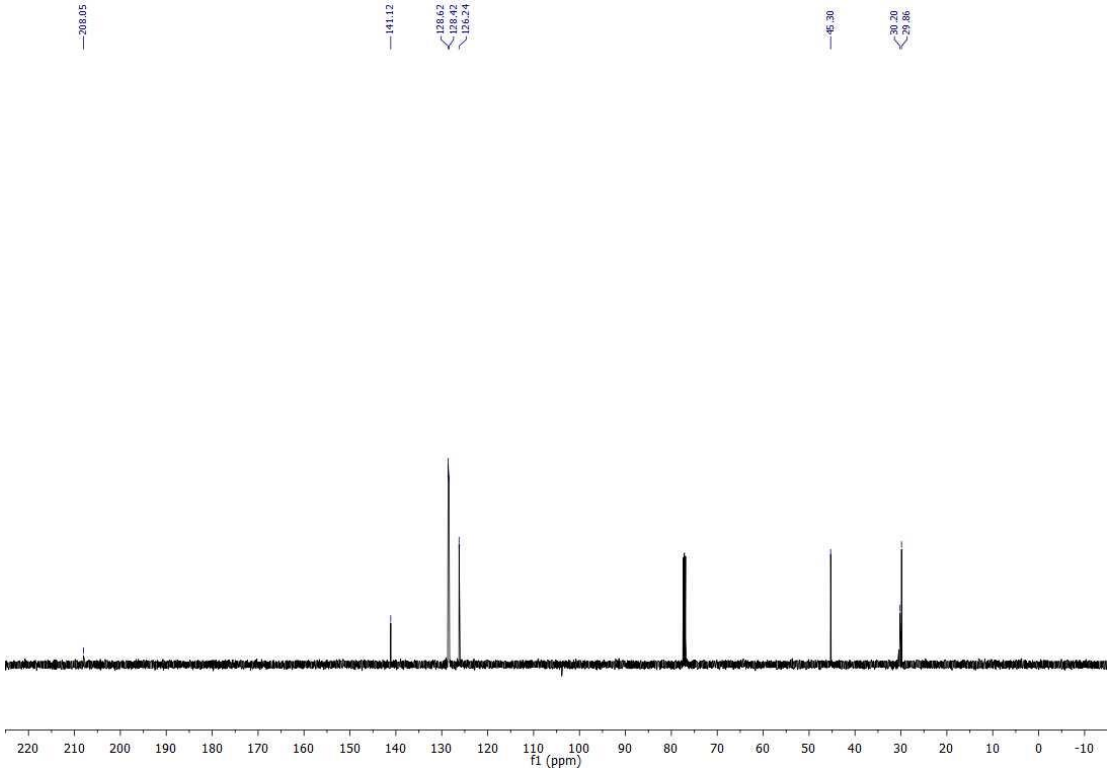
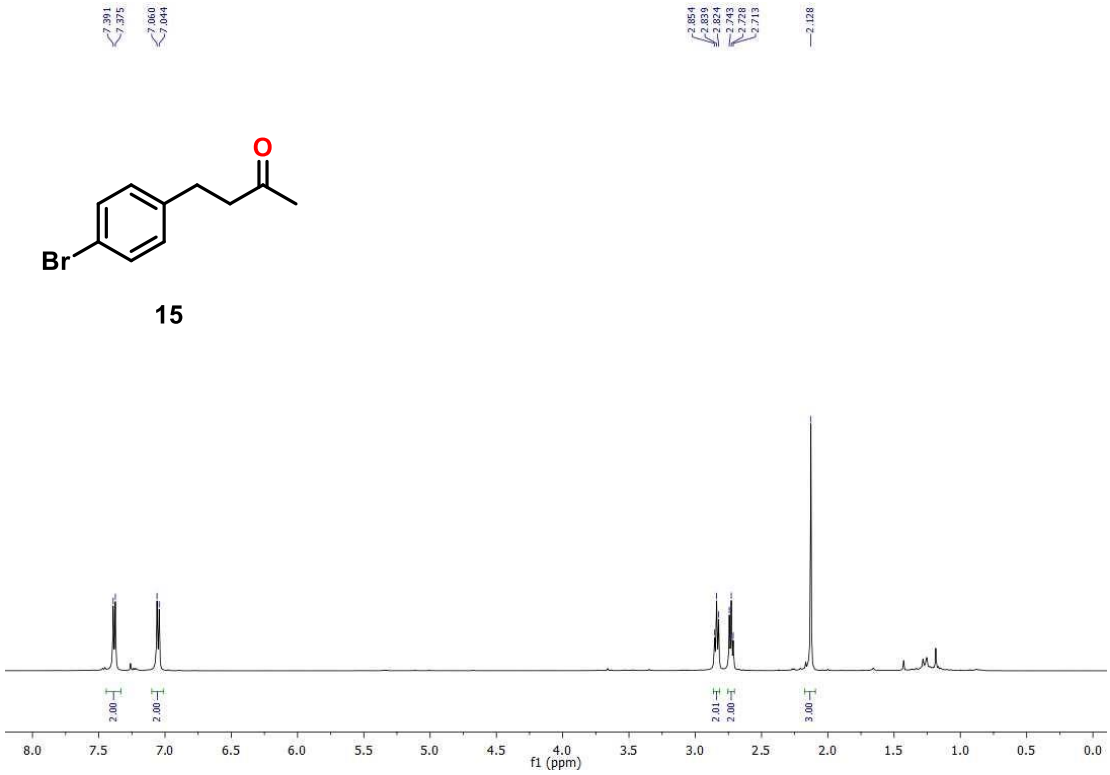
7.30
7.29
7.29
7.29
7.28
7.27
7.27
7.27
7.27
7.21
7.21
7.20
7.19
7.19
7.18
7.18
2.92
2.90
2.89
2.78
2.77
2.75
2.14
O
14
2.01
3.00
2.00
2.00
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


208.05
141.12
128.62
128.42
126.24
45.30
30.20
29.86
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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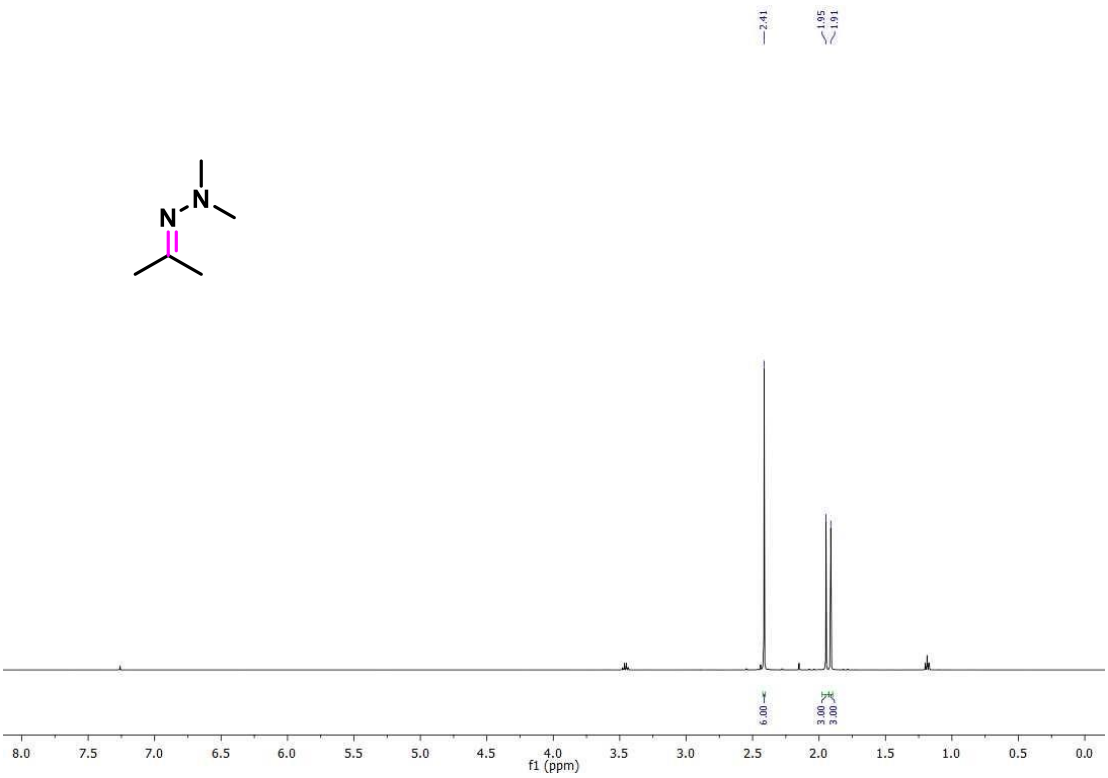
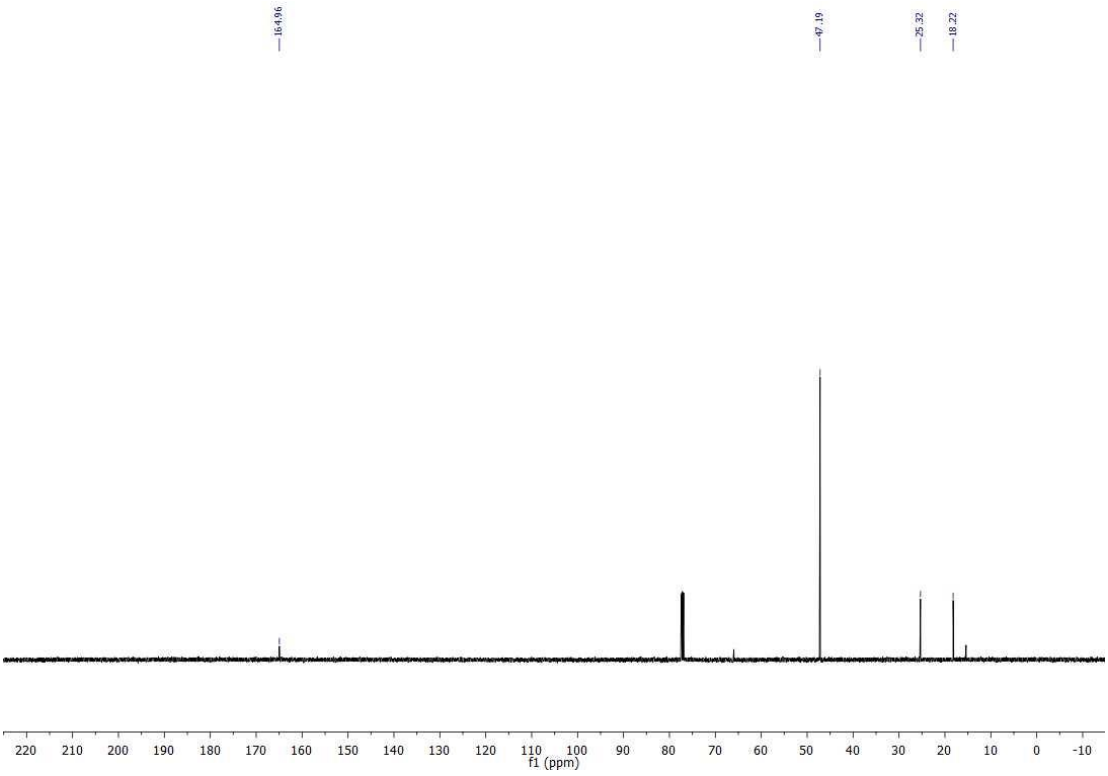
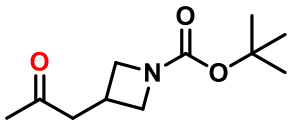
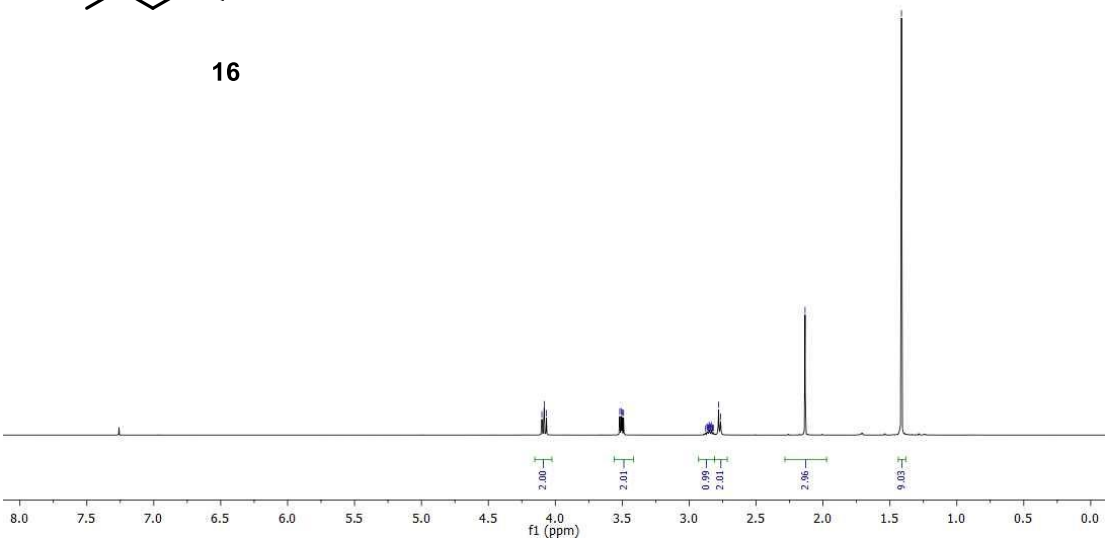
7.375
7.060
7.044
2.854
2.839
2.824
2.743
2.728
2.713
2.128
O
Br
15
2.00
2.00
2.01
2.00
3.00
f1 (ppm)
207.53
140.14
131.66
130.24
120.01
44.95
30.22
29.17
f1 (ppm)

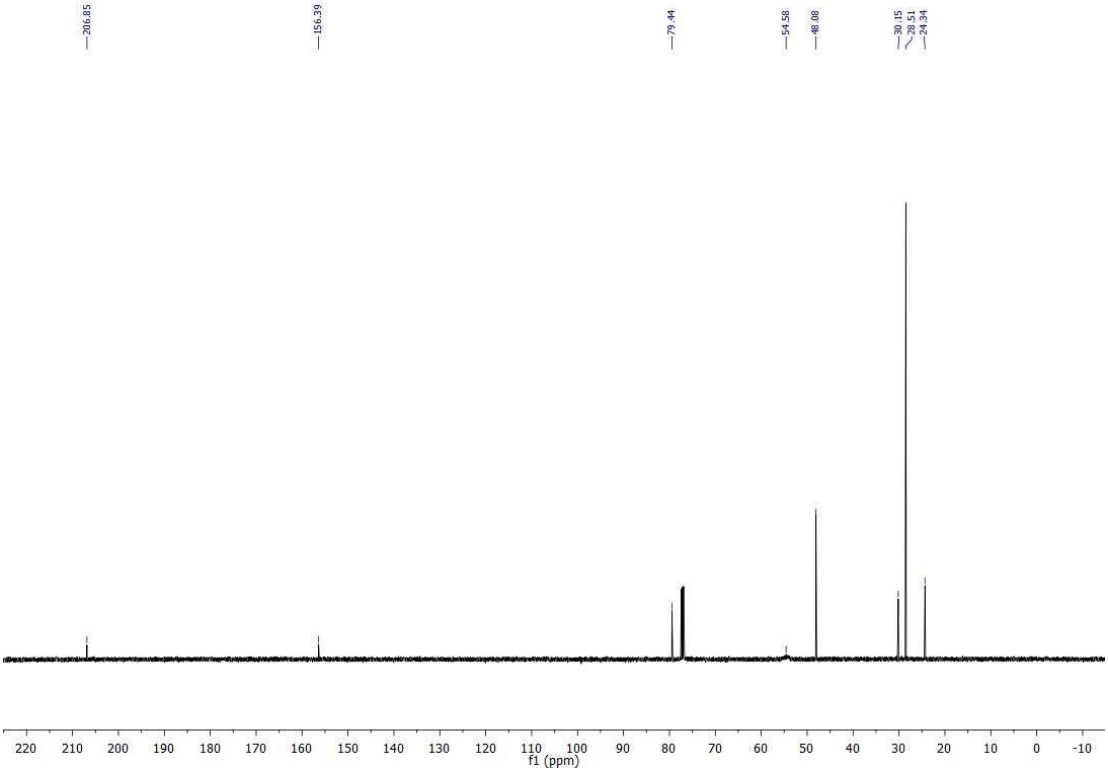

2.41
1.95
1.91
N
N
6.00
3.00
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


164.96
47.19
25.32
18.22
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



16


4.10
4.08
4.07
3.52
3.51
3.50
3.49
2.88
2.87
2.86
2.86
2.86
2.85
2.85
2.84
2.84
2.83
2.82
2.82
2.78
2.77
2.13
1.41
2.00
2.01
0.99
2.01
2.96
9.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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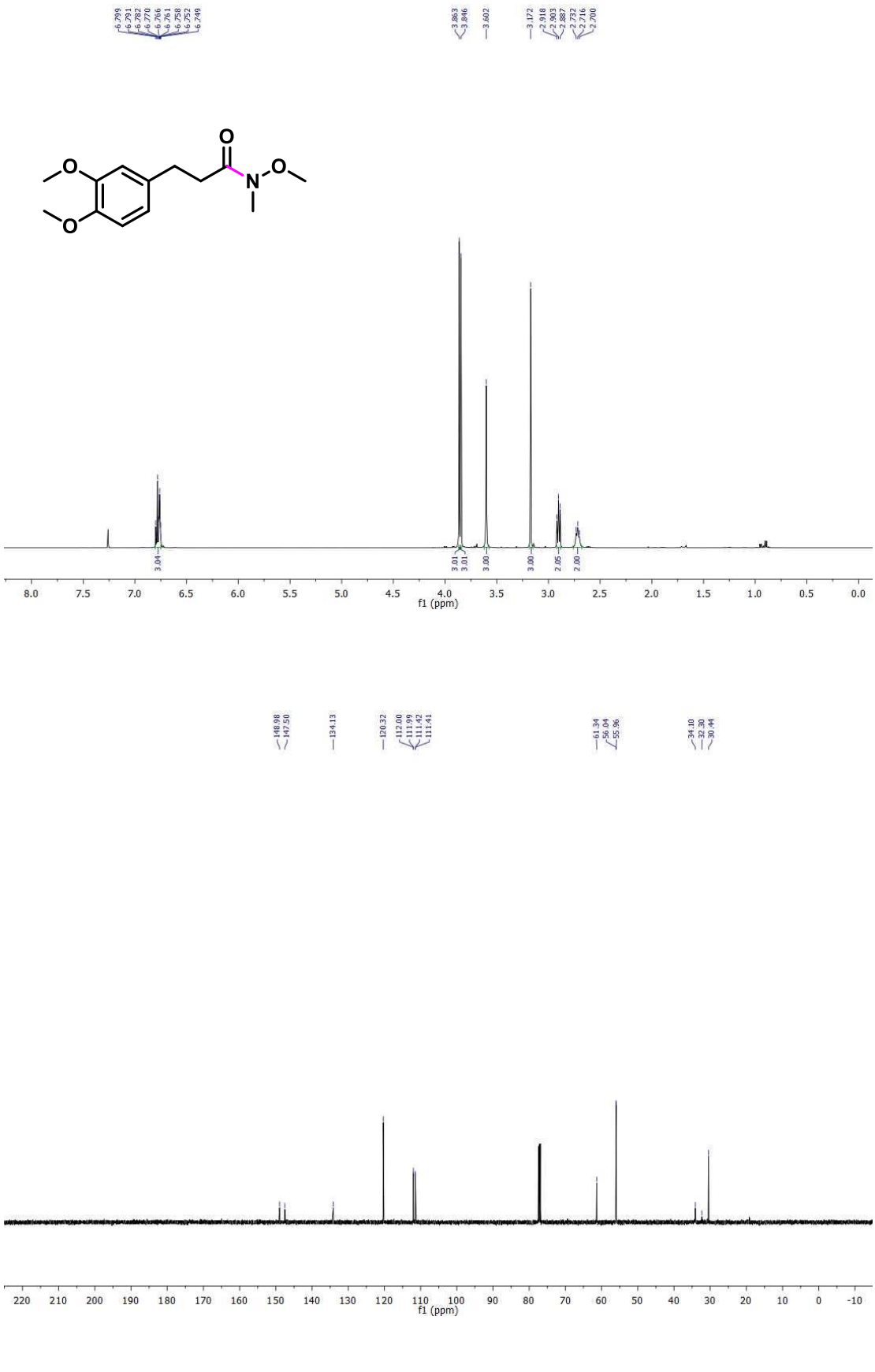
156.39
79.44
54.58
48.08
30.15
28.51
24.34
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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6.782
6.770
6.766
6.761
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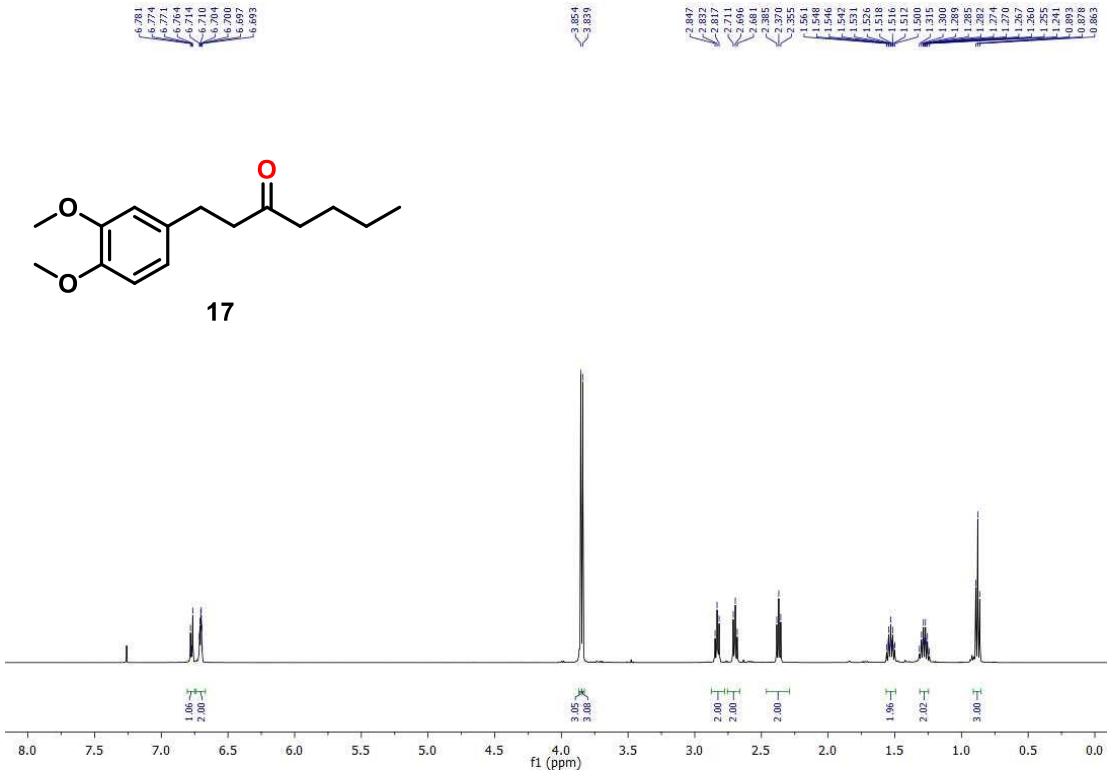
6.752
6.749
3.863
3.846
3.602
3.172
2.918
2.903
2.897
2.732
2.716
2.700
O
O
O
N
O
3.04
3.01
3.01
3.00
3.00
2.05
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
148.98
147.50
134.13
120.32
112.00
111.99
111.42
111.41
61.34
56.04
55.96
34.10
32.30
30.44
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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6.771
6.764
6.714
6.710
6.704
6.700
6.697
6.693
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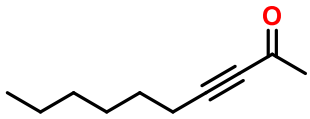
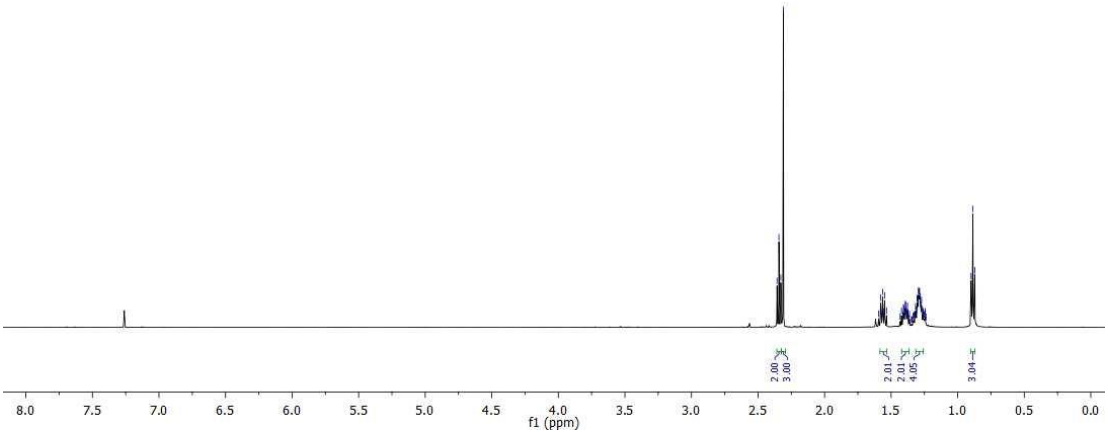
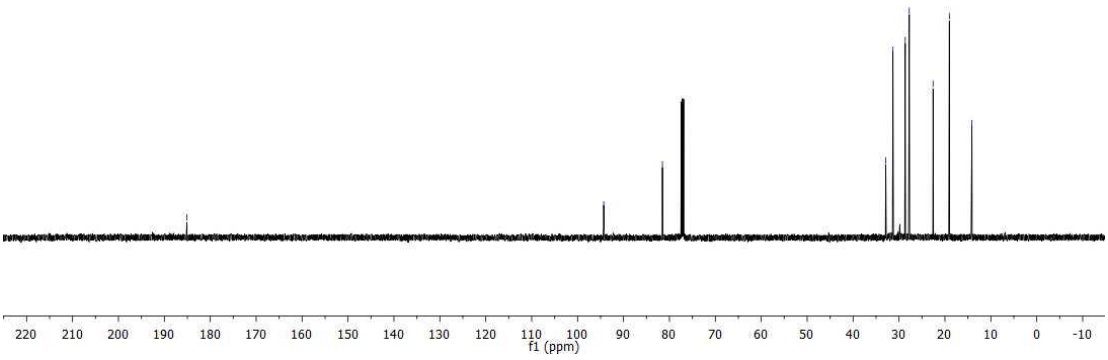
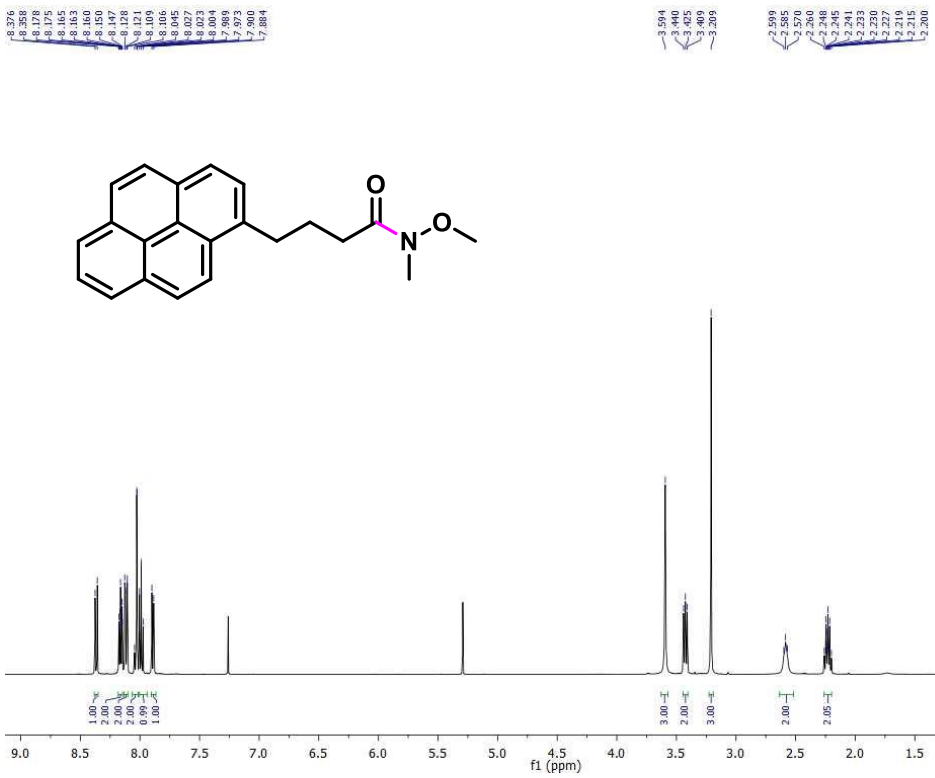
3.839
2.847
2.832
2.817
2.711
2.696
2.681
2.385
2.370
2.355
1.561
1.548
1.546
1.542
1.531
1.526
1.518
1.516
1.512
1.500
1.315
1.300
1.289
1.285
1.274
1.270
1.267
1.260
1.255
1.241
0.893
0.878
0.863
O
O
O
17
1.06
2.00
3.05
3.00
2.00
2.00
2.00
1.96
2.02
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
210.58
148.97
147.46
133.95
120.19
111.85
111.41
56.03
55.93
44.60
42.93
29.56
25.99
22.43
13.94
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

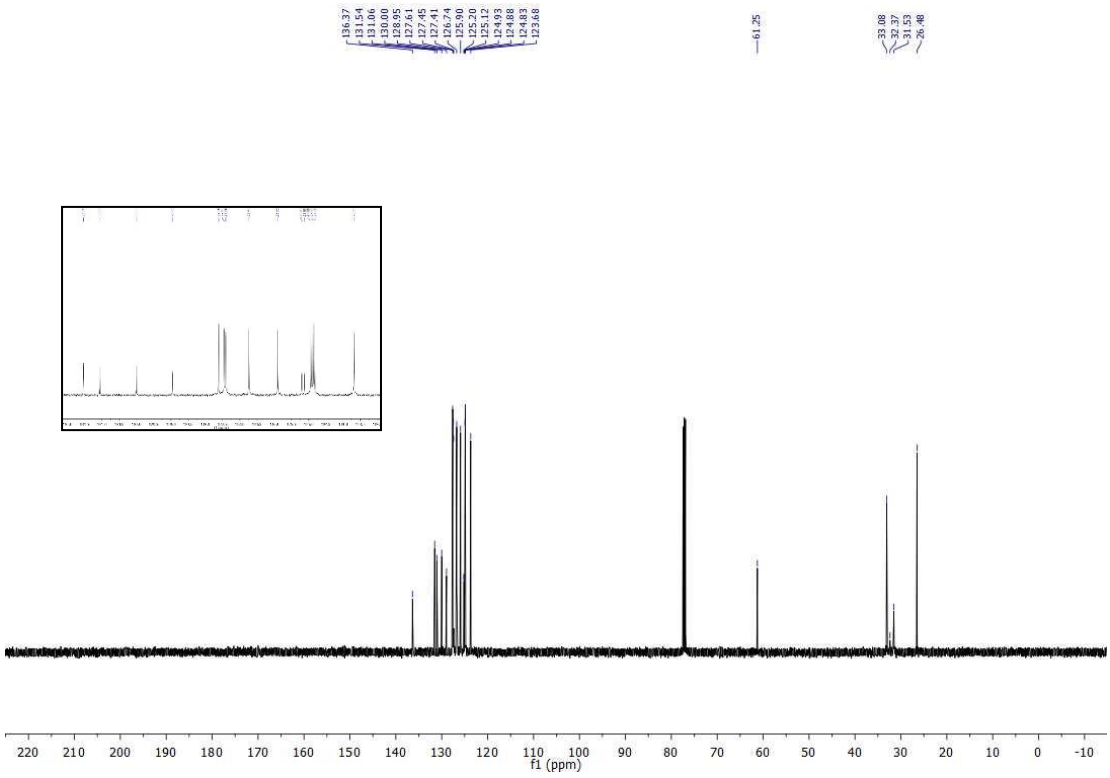


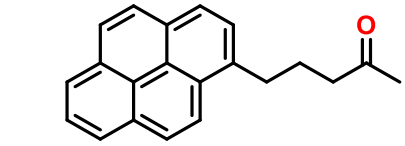
18


2.00
3.00
2.01
2.01
4.05
3.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
N
O
f1 (ppm)


f1 (ppm)



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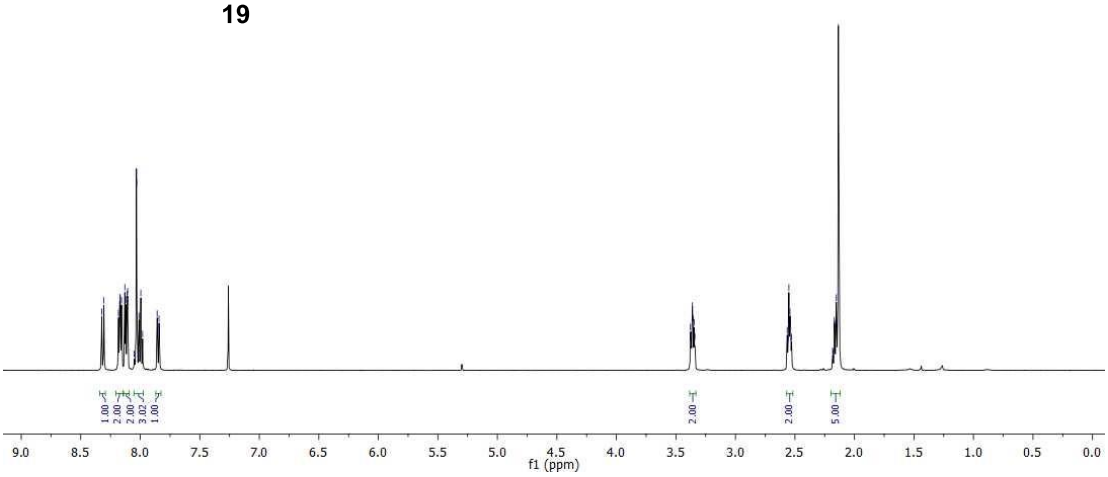
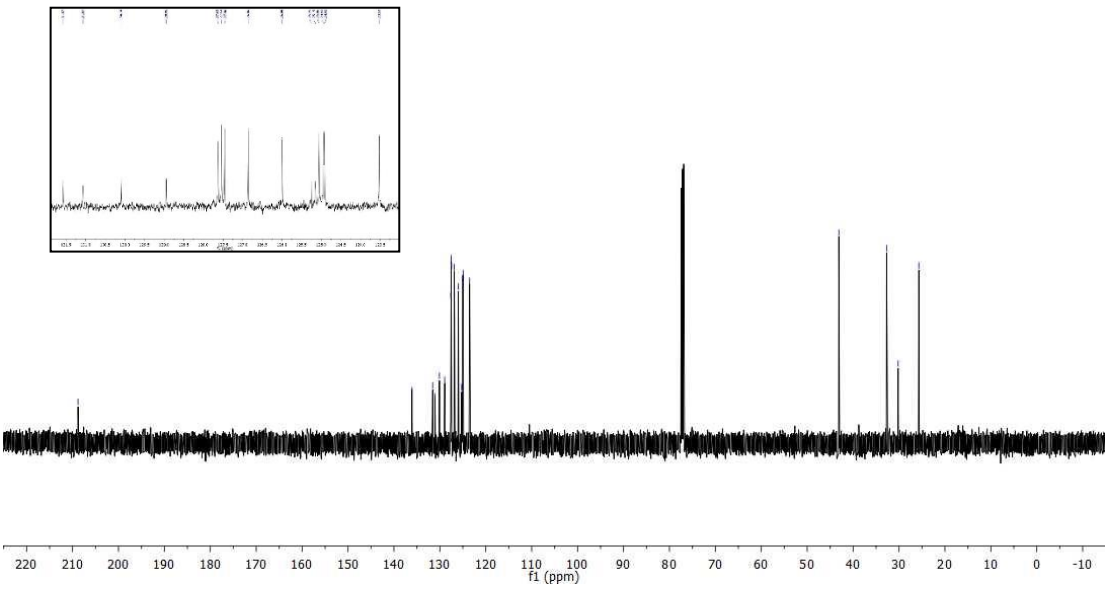
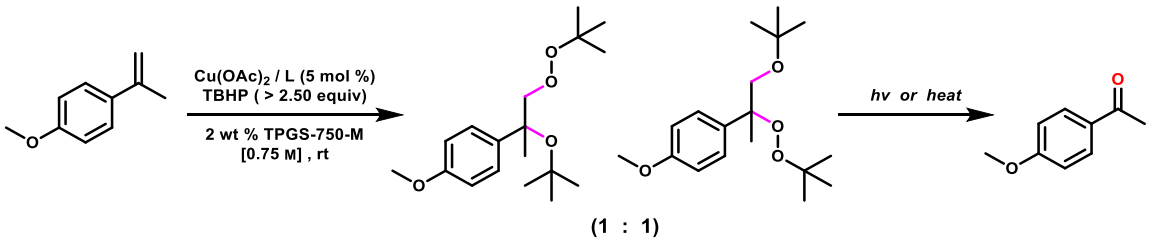


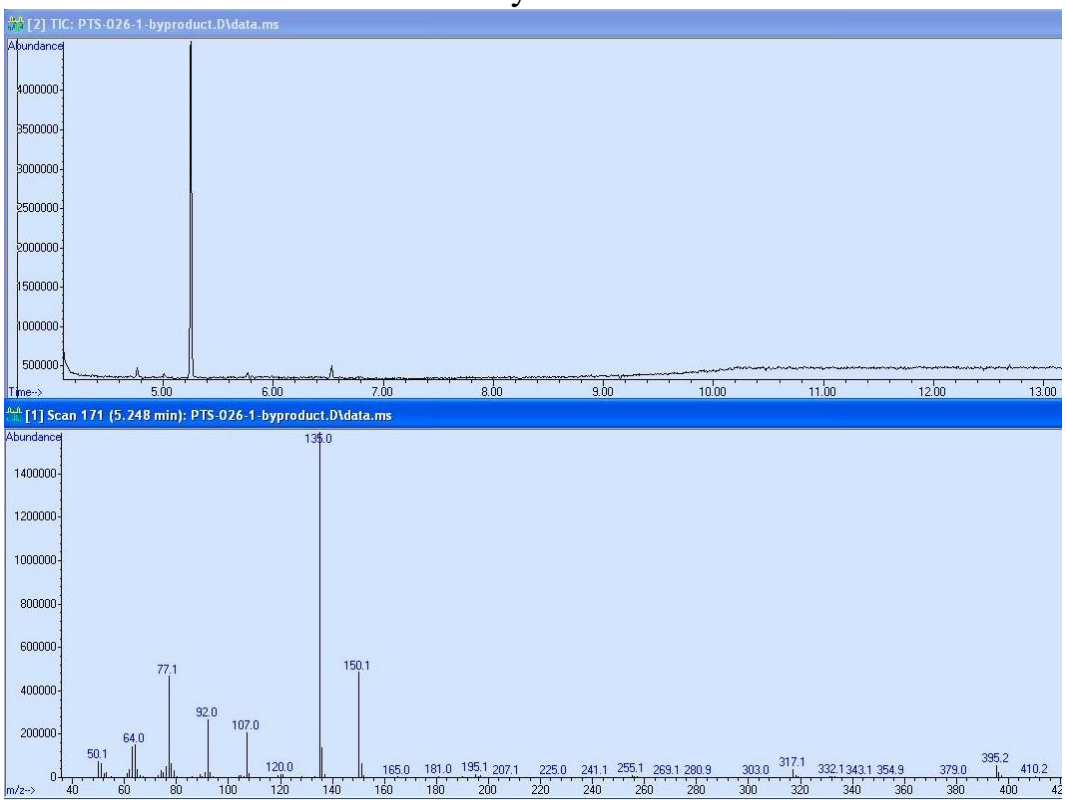


Kharasch Experiments:

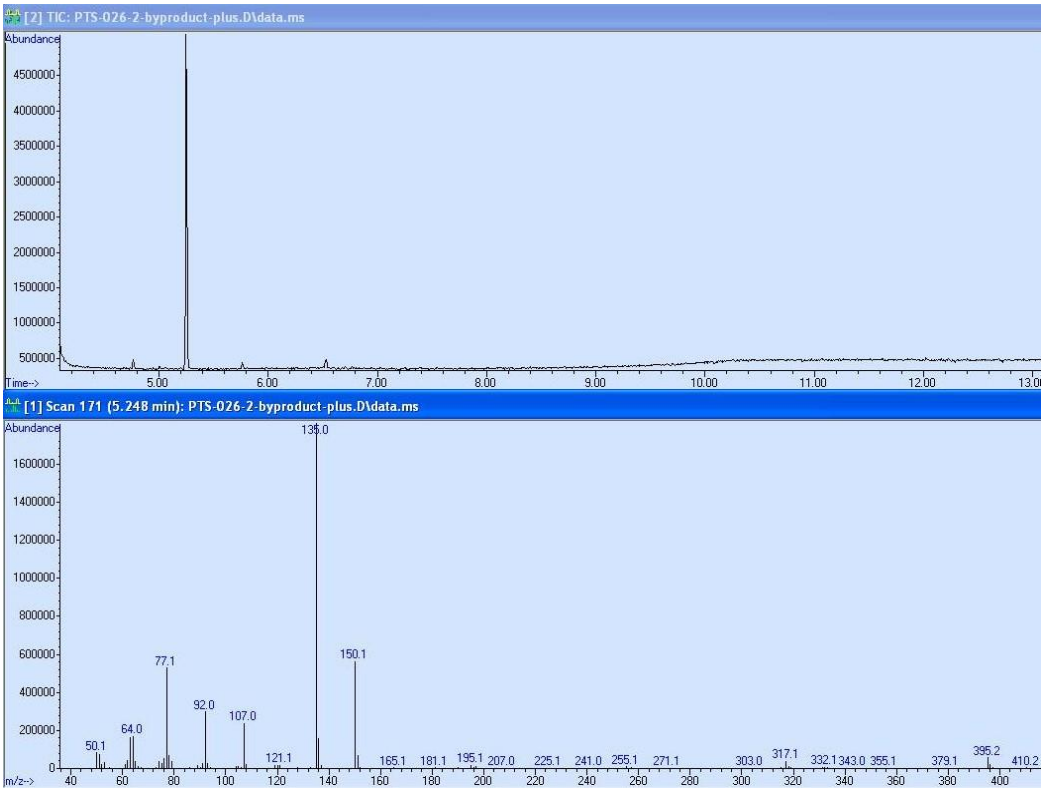


GC/MS Chromatograms: of Pure 'By-Product' and a ~1:1 Mixture of 'By-Product' and Authentic Ketone: Both Show a Single Peak with an *m/z* Corresponding to the Desired Ketone.

Pure 'By-Product'



A. Mixed: Same Pure 'By-Product' Sample + Authentic Ketone



Heat-Gun Experiment: ^{1}H-NMR Spectra Over